DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

# CIRCULATORY SYSTEM DEVICES PANEL

Wednesday, October 23, 2001

8:39 a.m.

Walker/Whetstone Room
Gaithersburg Holiday Inn
2 Montgomery Avenue
Gaithersburg, Maryland

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. TRACY: Good morning. I'd like to call to order this meeting of the Circulatory System Devices Panel.

We are going to start with a presentation from the Office of Surveillance and Biometrics on "Adverse Events and Deaths Associated with Hemostasis Following Cardiac Catheterization: Comparison of Manual Compression versus Collagen Plug and Suture Hemostasis Devices."

If the presenter is present, would he please take the podium?

Presentation by Office of Surveillance and Biometrics

DR. TAVRIS: Thank you.

This study was a collaborative effort between the FDA and the American College of Cardiology.

[Slide.]

Over the 5-year period between 1996 and 2000, 1,880 reports of serious injuries and 36 reports of deaths associated with the use of hemostasis devices used to prevent bleeding from the femoral artery following cardiac

catheterization were reported to the FDA through its medical device reporting system.

Most of these serious injuries and deaths involved hemorrhagic complications. It was also of interest that a large majority of injury and death reports involved women, even though cardiac catheterization is more common in men than in women.

This study considered the earliest two types of hemostasis devices--the suture device, Perclose, and the two collagen plug devices, VasoSeal and AngioSeal.

Because of the continued receipt of adverse event reports involving injuries and deaths, the FDA was concerned about the safety of these devices. Of course, these reports themselves do not causally implicate these devices in the injuries and deaths, since these can also occur following manual compression, in which case the events would not be reported to the FDA.

But the medical literature on this subject also gave us cause for concern. Of 13 studies that we could find that utilized manual compression control groups to assess risk of serious injury associated with hemostasis device use, 9 showed no

difference in the rate of adverse events between device users and controls, and 4 demonstrated a higher rate in device users. None demonstrated a higher rate in controls than in device users.

Two important weaknesses of the studies found in the medical literature are small sample sizes and the use of a single or small number of institutions. For example, the 13 studies referred to above utilized a total of 19,582 procedures, including a little over 15,000 controls and a little over 4,000 device users. Most involved a single institution.

By contrast, this study, which utilized the American College of Cardiology's National Cardiovascular Data Registry, involved 214 participating institutions and 166,680 procedures, including over 113,000 controls and over 53,000 device users--more than 7 times as many controls and 13 times as many device users than all the other studies combined.

This study included information from all cardio catheterization lab admissions representing the 214 institutions included in the ACC's data registry from the year 2001. Excluded from the analysis were outpatients and any patient for whom

critical data was not available.

Outcomes assessed in these analyses included hemorrhage, arterial occlusion and loss of arterial pulses, artery dissection, the development of an AV fistula or pseudo-aneurysm, and death associated with any of these events. Hemorrhage, by far the most common of these events, was defined as "blood loss requiring transfusion or prolonging the hospital stay or causing a drop in hemoglobin of greater than 3."

Stepwise backward multiple logistic regression analysis was performed in order to control for the effects of potential confounding variables. The main independent variable of interest was hemostasis device use.

Potential confounding variables that were assessed included demographic variables, comorbid conditions, type of procedure--that is interventional versus diagnostic cardiac catheterization--presence of left main coronary artery stenosis, and indications for the procedure.

Of the more than 160,000 subjects in this analysis, by far the most frequent complication was hemorrhage. There were 1,756 episodes of this, a rate of 1.1 percent. This represented 73 percent

of the subjects who were characterized by any adverse event in this study.

The mortality rate for the 2,418 subjects in this study reported within the adverse event was 5.5 percent.

First, I will present only the multivariate results that used the reporting of any adverse event as the outcome. Female gender and the use of interventional as compared to diagnostic cardiac caths were found to be the biggest risk factors, both with odds ratios of 2.3.

Several comorbid conditions and indications for the procedure were also found to be associated with adverse events. These included an emergency indication for the procedure, plaque as an indication for the procedure, acute myocardial infarction, history of renal failure, New York Heart Association class, and peripheral vascular disease, all with odds ratios between 1.2 and 1.8.

The use of a hemostasis device was found to be protective as compared with the use of no device, especially the use of the collagen plug devices, which demonstrated an odds ratio of 0.79, which was highly statistically significant.

[Slide.]

This table depicts odds ratios for those associations that were statistically significant at the P less than .05 level. To a large extent, the risks associated with any complication pertained to many of the specific complications as well.

Female gender was associated with five of the seven specific complications, all with odds ratios of greater than 2 and P values of .0002 or less.

The use of interventional cardiac catheterization was statistically associated with four of the seven specific complications.

Of the nine comorbid conditions or indications for the procedure that were assessed in this analysis, six of them were associated with three to five of the seven specific outcomes in the multivariate analysis. Those that weren't associated with these outcomes were probably precluded from this by their close association with the other comorbid conditions.

[Slide.]

As for the hemostasis devices, the most pronounced protective effect pertained to pseudo-aneurysms. Both types of hemostasis devices were characterized by odds ratios of approximately

one-half with respect to this outcome.

The hemostasis devices as a group demonstrated a protective effect with regard to hemorrhage, with an odds ratio of 0.89, although this protective effect was not statistically significant.

When the collagen plug devices alone were compared with manual compression, the odds ratio was 0.85 with a P value of .035.

Neither hemostasis device demonstrated a statistically significant protective effect with regard to vascular complication-related deaths. The collagen plug devices demonstrated an odds ratio of 0.56 with respect to this outcome, but because there was only a total of 144 of these deaths, the study was not powerful enough to attain statistical significance even with that low odds ratio.

The risks associated with female gender, interventional cardiac cath, and several of the comorbid conditions were not surprising, as these had been demonstrated previously. But we were surprised to note the protective effect of hemostasis devices given that concern over their safety was the main reason for conducting the study

and that the medical literature had generally shown them to be associated either with a greater than or equal risk of adverse events compared to manual compression controls.

Possible explanations for this apparent discrepancy are the following. First, confounding variables that were not controlled for in this analysis. However, this explanation seems unlikely to us given the large range of comorbid conditions that were controlled for in this study, although we did not control for coagulation status.

Second, it could be that the medical providers who participated in this study were more skilled in the use of these devices than most other medical providers. This is a complicated issue. On the one hand, that explanation is made less convincing by the large number of participating institutions in this study; but on the other hand, the protective effect seen in this study was not very great--only a 21 percent decrease in total complication rate for the collagen plug devices and a 15 percent decrease for Perclose.

None of the studies that we found in the medical literature was large enough to detect that small of a protective effect, even if one assumes

that the skill of the providers was comparable to that found in this study. But that would still not explain why a minority of studies in the medical literature have demonstrated a harmful effect associated with hemostasis device use.

Of course, since these studies generally involved a single institution, it is possible that the physicians involved in one or more of these studies were less experienced or skilled in the use of the hemostasis devices than average.

Finally, a third possible explanation for the protective effect found in this study compared with other studies is that over time, the users of these devices have become more skilled and thus more likely to produce better results than those seen in other studies.

That concludes my presentation, and I would be happy to answer questions.

DR. TRACY: Dr. Krucoff?

DR. KRUCOFF: Dale, with great respect for the noble intention here, I am really concerned that maybe we're just pouring worms into a can of worms.

In a nonrandomized platform there is an enormous bias involved in how you and when you

choose as an operator to use these things. Most of us will actually do a femoral injection before you position one of these, so anybody, where you are involved in a placque or at a bifurcation point or where you have had multiple sticks in a lesion, you don't even deploy these things.

So immediately in this kind of registry, there is an intrinsic bias just by case selection. And I would certainly list that amongst your possible explanations for the findings that you are looking at.

The other question I have is could you detail for us what you are aware of as far as any kind of quality control at the sites? Was the operator or somebody related to the operator who placed the device also the one who followed up on the patient and reported on complications, which of course is another source of bias--if you put one of these things in, you may tend to look at a little oozing or bleeding as just something that is going on in the tract because the patient is anticoagulated, whereas if you with manual compression have subsequent bleeding, you may report it differently.

How as the data quality-controlled at the

site level?
DR. TAVRIS: There were a number of quality control procedure that mostly included educational interventions to train the sites on how to record the data, and also overview of the data for completeness.
As far as potential bias in the recording of data, I'm not sure that any of the quality controls could have favorably influenced that.
The earlier comment about potential selection bias sets--part of what I meant when I talked about potential confounding variables that could have affected this--do you feel that the selection of patients would work in a way that would make the patients who received the devices a group that was less likely to experience complications?
DR. KRUCOFF: Definitely, absolutely, positively.
Lastly, you called this a "study." Did patients whose data were recorded in this registry provide informed consent?
DR. TAVRIS: I'm pretty sure they did. This was the American College of Cardiology's registry, and I'm pretty sure they did.

DR. KRUCOFF: We do not consent patients for registry data for the ACC.
DR. TAVRIS: Okay.
DR. TRACY: Dr. White?
DR. WHITE: Thank you.
I'd like to echo Dr. Krucoff's statement. As a user of these devices, I think you cannot underestimate the selection bias that goes into this compared to a randomized device trial. The published literature--our hands are tied about how patients are treated. You absolutely enroll the patients, they get one or the other, and you work very hard to make the patient fit the trial.
In our regular practice, however, we don't poke skunks with sticks. If that groin doesn't look good, it doesn't get a device, and we don't look for that trouble, and I think that is a major reason to explain why it appears that devices are safer.
The other thing is I think you may not completely understand the ACC Data Registry, which is a very voluntary, self-selected population. It certainly isn't a widely-adopted process. It doesn't even represent a majority of the catheterization laboratories in the U.S.--not

because it's not a good thing, it's just that it is expensive. For example, in my institution, I would love to participate, and my institution cannot afford to participate. So there is a lot of data missed, I think, if that is the database.

Then, finally, I think that that database is used for quality control, not for scientific generally reporting, so I think patients generally are not consented that their data would be collected and used. And I'm not sure what the implications are for that in terms of informed consent and the use of the data. That would be something that would be of concern, I think, to my local IRB that release of that kind of information.

DR. TRACY: Dr. Laskey?

DR. LASKEY: I would be very wary now and for the foreseeable future in using NCDR data. It is non-quality-assured. It is non-verified. There is no routine auditing as far as I can tell, as far as I know. And as Chris mentioned, it is an entirely voluntary registry which, maybe on one side of the coin bespeaks honesty on the part of the reporting sites, but it is extremely spotty, and-=

DR. TAVRIS: When you say "voluntary,"

doesn't that mean that it is voluntary as far as the institution, but the institutions that are participating in it do routinely collect data from all procedures?

DR. LASKEY: Yes, but the rigor with which that data is collected cannot be vouched for, and it will vary from site to site.

DR. WHITE: And the discipline should not be confused with the discipline for a randomized trial, which has audits, and you're pretty sure about that.

DR. LASKEY: It has become very fashionable in the last few years to do things like propensity scores and all that to try to adjust away for some of these biases in these observational trials. I would bet if you did that, you would still be left with the same answer, but it is probably worthwhile going through the exercise since you have a number of people who didn't get the device.

It has been our experience that it goes to more than the groin. If the groin or the artery doesn't look right, or if the patient doesn't look right at the end of the procedure, they do not get a closure device, either.

DR. TAVRIS: What data would you use to calculate the propensity scores?

DR. LASKEY: You have folks who got the device and folks who didn't get the device. That is your endpoint for the propensity score, and then you would put into the soup all the other variables that you just looked at as step one. And then, step two is to put the propensity scores into your final analysis. That is generally the way it is done. I am not supporting that as a way of verifying this data, but I think it is an interesting exercise.

DR. TRACY: You mentioned that there was an exclusion of outpatients. Does that mean outpatient caths, and procedures and interventions were excluded from analysis--because I think that in many institutions, most procedure are done as outpatient.

DR. TAVRIS: In this database, most of them were not outpatients, but yes, the data that I showed excluded outpatients although before we excluded them, we did analyze the data with outpatients in it, and we got very similar results.

The reason we excluded the outpatient afterward was that we felt that there might be some

potential for additional bias because there might have been disproportionate followup in one group or the other. We couldn't be sure how good the followup was.

DR. LASKEY: Dale, if available, just one other key variable which may not be in the database but that has clearly been associated with hemorrhagic complications is the extent of anticoagulation; what kinds of ACTs are in this patient population in a nonrandomized format.

Again, that may actually affect whether or not an operator would deploy a device, so you may have your higher ACTs on IIb/IIIa's in the wrong group.

DR. TAVRIS: We wanted to do that, but that data wasn't available. We do intend to do that in our next study. But from review of the medical literature, there is only one article, I believe, that did control for coagulation status, and in that article, those with hemostasis device use were more anticoagulated than those without use, and I would think that that would tend to make them look worse given that hemorrhage was the main complication here, and that group would have been more likely to experience higher hemorrhage rates.

So that would have contributed bias, I would think, in a direction that would have made our results, the protective effects seen for the hemostasis devices even less likely.

DR. TRACY: Dr. Zuckerman?

DR. ZUCKERMAN: Just by way of background, the Agency is always interested in ways of potentially addressing the pre- and post-market balance in terms of what we require pre-market before PMA approval of a hemostasis device versus post-market. And certainly this has been one attempt at looking at post-market datasets given the controversial nature of some of these devices.

Panel members have expressed problems with this particular registry, so the first question is are there any other datasets that might be useful to explore.

The second question refers to some of the implications of the panel discussion for our pre-market approval data requirements for these PMA hemostasis devices. Because there are large opportunities for selection bias, et cetera, our general standard has been to require a randomized trial versus manual compression.

Many sponsors have indicated that there is

a large historical database of manual compression results and have suggested other trial designs. I would be interested in any comments on how to evaluate these devices and with minimization of bias.

DR. KRUCOFF: I think one key question would be whether your issue is safety or efficacy. When you started the presentation, it seemed to me that the concern, because of the reporting mechanism that kicked all this in, was safety. And ultimately what your conclusions are leaning toward is are you demonstrating some kind of efficacy impact.

I would at least start by being clear on what the question that is being addressed is, and if complication rates associated with these devices are what you need to learn about, then I think you need to make sure that the data is collected in a way that you can understand whether the complication rates are higher than your target.

Now, in terms of manual compression, which I think has got to be the target, whether you could do a comprehensive job of characterizing an historic control where you understood that it was matched across important parameters to a study

population where that device is deployed, I don't think an historic control would be out of the question, but I think with this kind of registry, the trouble is you are absorbing a selection bias that probably has as much or more to do with any observed results. At least an historic control, you could try to structure to a population so you wouldn't have that kind of implicit bias.

DR. TRACY: It seems that maybe part of the problem is that there is selection bias for the type of device that is used in any given individual. It is going to be different, and the operator experience tremendously influences whether they do or do not use a particular device.

So I think that if there were a new device that was coming along, the only control that you could use would either be manual compression in perhaps the ACC database versus one of the approved device studies.

But I think it is just very difficult given the amount of bias that is inherent in this type of device to come up with a clean comparison.

DR. WHITE: I think the true value of this trial is not whether or not your operators are more skilled than the PMA published papers are, because

you can bet the people who are doing those trials are good at it. They wouldn't be doing those trials if they weren't fairly skilled, particularly at the randomized level. Those of us who do these trials get really good at these devices.

I am reassured that in real use, people aren't getting hurt with these devices, and they are able to select patients and perhaps use these devices to some optimum. I mean, the fact that you found some benefit here, or some lower risk, reassures me that people know how to use these devices to their optimal ability. In the randomized trials, you have really skilled operators doing the best they can, and it is sort of an even ground.

So I am reassured by your data, and I just think it means that out there in the real world, they are being used pretty well.

I don't think you can use historical controls, because the patient populations are so highly variable. Whether we are talking about diagnostic catheterization, interventional catheterization, the level of anti-coagulation are huge impacts, and you can make things look better or make things look worse depending upon how you

select. So the randomization here becomes a key.
Now, if you want to accept randomization against another closure device, that would be an interesting model if there is enough data to make you convinced that you know--if you want to randomize PercuSurge against the next level of device, that might be something I would be willing to do, but I would want to make sure that it was randomized so that the risks were evenly distributed in both populations.
DR. TAVRIS: I certainly agree that randomization would be by far a preferable way of looking at this. The problem is that what randomized data we have is very, very small and would not be able to detect small differences.
DR. WHITE: I agree.
DR. TRACY: Are there any other comments?
[No response.]
DR. TRACY: If not, thank you very much for that presentation.
We'll move on to the discussion of premarket notification of the Embol-X aortic filter.
MS. WOOD: The following announcement addresses conflict of interest issues associated

with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda for this meeting and all financial interests reported by the Committee participants. The conflict of interest statutes prohibit Special Government Employees from participating in matters that could affect their or their employers' financial interest.

The Agency has determined, however, that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the Government.

Therefore, a waiver has been granted for Dr. Thomas Ferguson for his interest in a firm that could be affected by the Panel's recommendation. The waiver involves a grant to his institution for the sponsor's product study in which he had no involvement and for which funding was less than $100,000 per year. Copies of this waiver may be obtained from the Agency's Freedom of Information Office, Room 12A-15, in the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the

agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. TRACY: Thank you.

I'd like to ask the panel members to introduce themselves, starting with Mr. Morton.

MR. MORTON: My name is Michael Morton. I am the industry representative, and I am employed by Soren Kolb [phonetic] Cardiovascular.

DR. WHITE: Good morning. My name is Chris White. I am an interventional cardiologist from the Ochsner Clinic in New Orleans.

DR. LASKEY: I am Warren Laskey, an interventional cardiologist from the National Naval Medical Center in Bethesda.

DR. KRUCOFF: I am Mitch Krucoff, an interventional cardiologist from Duke University.

DR. AZIZ: I am Samil Aziz, adult cardiac surgeon in Denver and associate clinical professor

at the University of Colorado.

DR. DeMETS: I am David DeMets. I am a biostatistician at the University of Wisconsin in Madison.

DR. TRACY: I am Cindy Tracy. I am an electrophysiologist at Georgetown University Hospital.

MS. WOOD: Geretta Wood, Executive Secretary.

DR. EDMUNDS: I am Hank Edmunds, University of Pennsylvania, a surgeon.

DR. MARLER: I am John Marler, Associate Director for Clinical Trials at the National Institute of Neurological Disorders and Stroke, and I am a neurologist.

DR. FERGUSON: Tom Ferguson, a cardiac surgeon at Washington University in St. Louis.

DR. PINA: Ileana Pina, heart failure transplant cardiologist, Case Western Reserve in Cleveland.

MR. DACEY: Robert Dacey, Consumer Representative, from Boulder County, Colorado.

DR. ZUCKERMAN: Bram Zuckerman, Director, Division of Cardiovascular Devices, Food and Drug Administration.

DR. TRACY: Thank you.

MS. WOOD: Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as voting members of the Circulatory System Devices Panel for this meeting on October 23, 2002: Christopher White, M.D.; L. Henry Edmunds, Jr., M.D.; Mitchell W. Krucoff, M.D.; John Marler, M.D.; Thomas B.Ferguson, M.D.; David L. DeMets, Ph.D.

For the record, these people are Special Government Employees and are consultants to this panel and other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This is signed by David W. Feigel, Jr., M.D., M.P.H., Director, Center for Devices and Radiological Health, and dated October 10, 2002.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health dated October 27, 1990 and as amended August 18,

1999, I appoint the following individual as a voting member of the Circulatory System Devices Panel for the meeting on October 23, 2002: Ileana L. Pina, M.D.

For the record, Dr. Pina is a consultant to the Cardiovascular and Renal Drugs Advisory Committee of the Center for Drug Evaluation and Research. She is a Special Government Employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

This is signed by William K. Hubbard, Senior Associate Commissioner for Quality Planning and Legislation, and it is dated October 18, 2002.

DR. TRACY: Thank you.

At this point, we'll move to the open public hearing. There were no scheduled speakers, but is there anyone in the audience who wishes to address the panel on today's topic or any other topic?

[No response.]

DR. TRACY: If not, we will close the open public hearing and move on to the presentation.

MS. WOOD: I would just like to remind the speakers to introduce yourself and state your

conflict of interest.

Sponsor Presentation

EMBOL-X, Inc.

K022071, EMBOL-X Aortic Filter

MS. CHANG: Thank you.

My name is Jean Chang. I am the Chief Operating Officer for EMBOL-X, and I would like to thank the FDA, our panel reviewers, and all panel members for the opportunity to present our clinical results today.

[Slide.]

This is the presentation that we have planned. After I do a company overview, Dr. Nicholas Kouchoukos, Missouri Baptist Medical Center, the co-principal investigator, will give an overview of atheroembolism in cardiac surgery.

Dr. Richard Kuntz, from Brigham and Women's, will present our EMBOL-X clinical trial design.

And finally, Dr. Keith Allen, who is the site PI at Saint Vincent, will present the clinical study results.

[Slide.]

EMBOL-X is a small, privately-funded company that was founded in 1996 by two physicians.

It is in Northern California, and has less than 50 employees.

The product focus from the start has been intra-aortic filtration utilized during cardiac surgical procedures.

The first clinicals were done at the end of 1997; CE marked the product in the end of 1998. And the product has been commercially available in Europe since 1999, with over 2,000 documented cases.

[Slide.]

What we show here are the two devices that make up the EMBOL-X intra-aortic filtration system. The top device there is the EMBOL-X aortic cannula, which has the premarket [inaudible] this past September is a modified standard cannula.

The bottom device is the subject of our presentation, which is the EMBOL-X intra-aortic filter. The distal filter basket there is composed of two primary components. It is a polyester mesh with 120 microns, and the polyester mesh is heparin coated with a duraflow heparin coating, which is the same heparin coating that is used [inaudible] filters.

What this demonstrates is the principle of

use of the filter in cardiac surgery. It has been inserted through the sideport in the cannula, and again, as you will note here, the filter captures particulates that arise from the heart up to and proximal to the arterial cannula. It does not capture particulate that is distal to the cannula, including arterial flow.

What you see on the right there is a representative sample of the particulates that are captured. The grid marks there are 3 mm, and Dr. Allen will talk more about particulate capture as we go forward.

[Slide.]

Embolic protection, embolite capture, is not a new technology, and the EMBOL-X intra-aortic filter follows along the same lines as existing devices that are either currently approved or under investigation. And as we discussed earlier, the extracorporeal filter is standard in cardiac CPB surgery. The PercuSurge distal protection device is used for SVG, and Dr. Kuntz will talk a little about that.

And finally, in other arterial beds, there are other distal filtration devices that filter particulate emboli in the [inaudible] vein area

graft, which is for carotid intervention.

And finally, in a different area, there are vena cava filters.

[Slide.]

All these devices capture particulate emboli, and it is the basis for the indications for our device. "The EMBOL-X aortic filter is indicated for use with the EMBOL-X aortic cannula in cardiac surgery procedures to contain and remove particulate emboli." This is the basis for our clinical study design and for the clinical study results which you will hear later on today.

I would now like to present Dr. Nicholas Kouchoukos from Missouri Baptist.

DR. KOUCHOUKOS: Thank you very much, Madam Chairman, members of the panel.

I am Nicholas Kouchoukos from the Missouri Baptist Medical Center in St. Louis, Missouri. I served as the co-principal investigator in this trial and was the principal investigator at the Missouri Baptist Medical Center.

I have no financial interest in the company or any equity investment in the company. I have been reimbursed for my travel expenses, and a grant on my behalf for services rendered has been

made to the Educational Research Foundation of the Missouri Baptist Medical Center.

[Slide.]

Since the beginning of open heart surgery, employing cardiopulmonary bypass has been recognized, and embolization of atheromatous debris from the atherosclerotic aorta is a cause of strike and other embolic-related complications.

Until the last decade, there were scattered case reports implicating atherosclerosis. In 1992, in a landmark study published from the Cleveland Clinic by Christopher Blauth and colleagues, they autopsied 221 patients who had died following cardiac surgical procedures, and they observed a high prevalence of atheroembolism in these patients and were able to correlate the presence of atheroembolism with increasing age and aortic atherosclerosis, as well as the presence of peripheral vascular disease.

[Slide.]

Among the patients with atheroembolism who had atherosclerosis of the ascending aorta, the presence of atheroembolism to various organs was 37 percent; among the patients who had no significant atherosclerosis, the prevalence was 2 percent.

This was a highly significant difference.

[Slide.]

There was a high correlation with increasing age and the presence of atherosclerotic disease in the ascending aorta.

In a clinical trial we conducted at Washington University in St. Louis using epiaortic scanning to determine the severity of atherosclerosis in the ascending aorta, we also observed a substantial correlation between increasing age and the prevalence of severe atherosclerosis in the ascending aorta.

Among the patients over the age of 80, for example, 33 percent of the patients had moderate or severe atherosclerosis.

[Slide.]

The prevalence of other risk factors for increased mortality and morbidity in patients undergoing cardiac surgical procedures such as coronary bypass grafting has increased over time.

This is a study from the Society of Thoracic Surgeons Database looking at a subset of Medicare patients, that is, those over the age of 65, and looking at the prevalence of important risk factors for mortality and morbidity over a decade

between 1990 and 1999. This involved over 620,000 patients.

In this analysis, there was a substantial increase in many of the important risk factors associated with mortality and morbidity.

[Slide.]

This is an example of atherosclerosis in the ascending aorta with very friable material located circumferentially in this aorta, and this is the material that is at risk for dislodgement during cardiac surgical procedures where manipulation of the aorta with interventions such as cannulation or clamping is prone to dislodge this material.

[Slide.]

In the study by Blauth and colleagues looking at the organs that were affected with atheroembolism, the most common site was in the brain, and this was followed by the spleen and the kidney. This is not surprising because approximately 40 percent of the cardiac output is delivered to these two organs.

[Slide.]

These are some examples of small atheroemboli in the cerebral circulation, and

below, in the presence of a large atheroembolism in a medium-sized artery. These are cortical infarcts in a patient following cardiac surgical procedure, and again, a large embolus of atheromatous material present in one of the renal arteries.

[Slide.]

We also looked in the early 1990s at the association of atherosclerosis as a predictor and the development of postoperative renal dysfunction. The index of renal dysfunction was the elevation of the keratinine to a level above 2.0, or an increase of 50 percent from baseline. And we correlated these changes in renal function with the presence of ascending atherosclerosis determined by epi-aortic scanning.

There was a correlation with the severity of disease and the prevalence of renal dysfunction.

[Slide.]

The analyses were performed on Day 1 and Day 6, and using multivariate analysis on the first postoperative day, ascending atherosclerosis was the only independent predictor of renal dysfunction. On Day 6, it was one of three predictors of renal dysfunction, along with low postoperative cardiac output and preoperative left

ventricular dysfunction.

[Slide.]

There are a number of interventions which have been designed and implemented in an attempt to reduce the frequency and severity of embolization from the ascending aorta.

Extracorporeal filtration will remove embolic material, but it is not likely to remove any material from the ascending aorta.

The interventions that are commonly used are those that involve minimal manipulation of the ascending atherosclerotic aorta. The use of a single cross-clamp rather than placement of multiple clamps reduces the frequency of manipulation of the aorta and, presumably, the dislodgement of atheromatous debris.

The use of proximal anastomotic devices to avoid the placement of clamps on the aorta may have a protective effect.

The use of off-pump surgery avoids placement of clamps on the ascending aorta, and other techniques such as hypothermic fibrillation and circulatory arrest have been utilized, again, to avoid clamping and other manipulation of the ascending aorta.

Although these techniques may be effective, they have certain limitations. All of the atheroembolism cannot be eliminated with these techniques. For example, the proximal and anastomotic devices do involve manipulation of the ascending aorta with the potential for dislodgement. Off-pump surgery also involves manipulation of the heart and the aorta, despite the fact that no clamps are placed on the aorta.

Furthermore, there are other sources of emboli. The left atrial appendage can release thrombus; there can be neural thrombus in the left ventricular cavity that can be released, and also debris from diseased mitral and aortic valves, and also surgical debris.

The intra-aortic filter has the capacity to capture this debris as well.

[Slide.]

In a study by Dr. Denise Barbut and her colleagues, looking at embolization of particulate matter, they utilized transesophageal ecocardiography and transcranial doppler and identified the release of emboli during cardiac surgical procedures.

This is just the distribution of the

particle size of these emboli that were released in a study in 10 patients. And above is shown the diameters of various vessels in the intracranial circulatory system--the leptomeningeal vessel, the small cortical arteries, the posterior cerebral artery, the branches of the middle cerebral, and here, the larger middle cerebral artery and the internal carotid artery.

The diameters of these particles corresponds to the diameters of these arteries.

[Slide.]

In another study, Dr. Barbut and her colleagues looked at the temporal sequence of release of emboli from the aorta during the conduct of a cardiac surgical procedure. They found that the majority of these particles were released at the time of the release of the aortic cross-clamp from the ascending aorta.

In fact, over 70 percent of the emboli were released in 20-second interval following the release of the clamp. This is the rationale for inserting the intra-aortic filter just before release of the aortic clamp during the cardiac procedure.

[Slide.]

As I have indicated, there are important complications that can result from atheroembolism.

Stroke is the one that has caused the greatest concern because of the important mortality and morbidity that results from stroke. And it is now clearly recognized that atheroembolism is the principle cause of stroke following cardiac surgical procedures.

There is also evidence for renal and other organ system dysfunction. Pathologic and clinical studies that we have presented suggest that embolization may be an important cause of renal dysfunction postoperatively.

Embolization is also a possible contributing factor to postoperative neurocognitive dysfunction.

There have been strategies employed to reduce serious embolic-related complications. Obviously, prevention would be the best option, and this would involve minimal or no manipulation of the aorta, but this is not 100 percent effective in eliminating embolization.

Resection of the diseased aorta is a way to eliminate the emboli, but is only applicable to a very small percentage of patients.

Reduction of the embolic load is an attractive way to reduce this embolization.

Diversion is one option, to divert the material away from the central nervous system, but this would merely disseminate this material to other organs.

And capture, using an intra-aortic filter, is an attractive method for capturing this embolic material.

[Slide.]

In the subsequent presentations, Dr. Kuntz and Dr. Allen will discuss the design and execution of a large, randomized clinical trial evaluating the safety and efficacy of the EMBOL-X intra-aortic filter. This study is well-designed, in my opinion, and clearly demonstrates that use of the EMBOL-X filter is a rational, safe, and beneficial intervention for removal of atheromatous and other embolic material from the ascending aorta of cardiac surgical patients.

Thank you.

DR. KUNTZ: Good morning. My name is Rick Kuntz. I am a cardiologist at Brigham and Women's Hospital in Boston.

I got involved with this group about 3

years ago because of my interest in designing and working with trials on embolic protection in the heart, in the brain, and in the kidney. This afforded me an opportunity to work with a company who was looking at another way to impact on the reduction of embolic problems associated with cardiac surgery.

My interest in this study is mainly academic. I have no financial interest in the company. I have no equity. I am being reimbursed for my travel, and a small grant was made to the Department of Medicine on behalf of this consultation.

[Slide.]

The purpose of this study--and I am going to talk about the rationale as to how we came up with the design for the study--was from the outset to demonstrate the ability of this device to safely and effectively remove visible particulate emboli during cardiac procedures.

So at the outset, there was an assumption that these particles were bad--that they floated around in the bloodstream, that they would be released with the cross-clamp, and that they probably don't do good things if they go around the

arch of the aorta.

So from the beginning, it was important to understand that we were trying to remove these things, and how to measure them clinically was the biggest challenge in trying to design the trial.

[Slide.]

So the goal was to design a clinical trial that evaluates the utility of the device aimed to prevent the dissemination of released emboli following cross-clamping.

Now, here is the dilemma. We have particles that we can pull out, but the question is going to be what will these particles mean--is it really important to take them out or not. So the bet way to correlate that is to try to find hard clinical endpoints that could be collated overall. And we were struck with trying to design a trial to demonstrate that, because we were dealing with a problem of embolic showers that might not manifest themselves as frank organ infarctions.

So for example, if you have small particulate emboli that cause microvascular injury--organs such as the brain, the kidney, the spleen, and others--it might not be demonstrated as a frank, say, NIH-level major stroke or as a kidney

infarction.

And there was some stuff that we had learned from heart trials which I will talk about in a second, but ultimately, this was the biggest issue we had to deal with.

One of the potential roles in looking at the impact of shower emboli was to measure cognitive dysfunction, and I will talk about the availability of instruments at the time of the trial design and whether there was consensus in the surgical community as to whether that could be applied or not.

So these various study designs were explored and discussed with the FDA, and ultimately, in multiple discussions at which I was present, the focus was to demonstrate safety of this device with removal of particulate emboli as some demonstration of efficacy.

Let me give you a parallel about the importance of shower emboli and how you can measure it in an organ that actually does give you a clinical outcome with shower emboli.

[Slide.]

There is a device on the market to protect emboli from intervention on vein grafts through the

heart. This is a picture of the typical amount of emboli that is removed in the vein graft intervention, and they are manifested mainly by outcomes measured by cardiac enzyme elevation.

So the heart is a nice organ, because it actually can show the impact of shower emboli, mainly manifested by elevations of cardiac enzymes.

[Slide.]

If we look at the primary endpoint of this study, which was 8 percent in those patients randomized to protection, where we actually removed particles, compared to nothing at all where particles were not removed, there was a 50 percent reduction in the major endpoint of the trial.

[Slide.]

But if we look at an index like frank organ infarction, which would be QMI, something we could pick up clinically, such as a change in the EKG or Q-wave, it only represented about 10 percent of the outcome. The majority of the outcome of this endpoint was measured by enzyme elevation which didn't manifest itself as a frank organ infarction.

So it is important to understand that at least in the heart, shower emboli do have an impact

that led to approval of the device, but wasn't mainly manifested in anything else other than a cardiac enzyme elevation.

[Slide.]

So if we look at this issue, the shower emboli from vein grant intervention, it does not usually manifest as a frank MI, and in the SAFER trial, the availability of cardiac enzyme rise is essentially used to show utility of the device.

This reduction in myocardial infarction led to the approval of the device, and I think there was a general consensus across the interventional community that this was a good thing to use and now is considered to be a standard of care for vein grant intervention.

Now, the same endpoints are also used in the heart to approve the whole classification of IIb/IIIa inhibitors. That is, another valuable, considered standard therapy, across our area was based on the reduction, mainly in emboli, that manifested themselves as cardiac enzyme elevations but not frank organ infarction.

This was not applicable to the EMBOL-X system because it was north of the heart; this device wasn't designed to protect emboli in the

coronary arteries following bypass surgery. And there were few parallel sensitive measures that were available for noncardiac end organs. That is, we don't have an enzyme elevation for the brian or for the kidney like we do for the heart to measure the impact of these emboli overall.

[Slide.]

So if we look at the distribution of organs that Dr. Kouchoukos showed that were targets for emboli from previous studies, we have a lot of important organs that we don't want in embolis, obviously, but we don't have good, readily available measures to demonstrate their injury pattern from shower emboli. And this was a conundrum that we were stuck with in trying to come up with an effective endpoint ultimately to demonstrate utility of this device by a clinical signal.

[Slide.]

So the issue raised by the FDA in our meeting was that there are few sensitive and specific measures available to look at the noncardiac end organs and their impact from shower emboli.

Neurological assessment was obviously a

very important one to evaluate, and there was much time spent look at all the available ways of looking at the neurological outcomes, because after all, the brain does receive approximately 20 percent of the circulation of the cardiac output and was obviously a target that we wanted to reduce.

Well, if we wanted to look at frank reduction in stroke, as Dr. Kouchoukos showed--that stroke is likely involved with emboli per se--the instance of stroke following cardiac surgery was large enough that this would have to be a very, very large sample size in order for us to demonstrate a reduction. Now, a 20 percent reduction is pretty small, but still, if you are looking for 30 or 40 percent, we are talking about 5,000 to 10,000 patients minimum to demonstrate a reduction in the 2 to 3 percent stroke rate seen postoperatively.

So what about measuring the cognitive function per se. Well, there are a lot of issues raised regarding using cognitive function as an endpoint in this study, and it is very controversial. First of all, the cell deficits may be due to diffuse small vessel embolism, to be

sure, but there are other multifactorial causes of cognitive dysfunction after surgery that may involve general anesthesia.

And even though it will be important to look at that at the time of the study and, I would even argue today to some degree, there is still no great consensus about instruments available for psychometric or neurological outcomes that measure cognitive dysfunction that has been accepted in the cardiovascular community, and at the time of this study, we couldn't get consensus along the lines of understanding whether to apply a battery of tests, most of which still have not been validated.

[Slide.]

So the practical approach was that the huge sample size to show a reduction of frank infarction such as stroke was just not feasible, because this is a large, randomized cardiac surgical trial, and it was unlikely that we could do a 5,000 to 10,000 patient study. Cognitive dysfunction could not be readily measured with mature, validated instruments was the conclusion that we reached in discussions with the FDA, and the proof of safety plus demonstration of captured emboli seemed to be the most feasible and logical

approach to go forward.

So when you look at this study to say why wasn't there a clear clinical measure of efficacy of this endpoint per se, it is because we wrestled with endpoints that had consensus to demonstrate true efficacy from a clinical perspective.

And the final conclusion was that we would demonstrate safety by the safety endpoints to demonstrate this didn't cause any increases in those elements in the safety endpoints. And if we demonstrated that with removal of actual particulate emboli, at least there would be some measure of utility. Now, whether the utility would be enough for product approval, I think will be the discussion of this panel.

Therefore, the approved IDE study design was safety equivalency for the composite primary endpoint and effectiveness through demonstration of particulate capture.

[Slide.]

So given that, there was a prospective study design; multi-center, 21 sites; a sample size of 1,289 patients was calculated using a Blackwater [phonetic] formula for equivalency of an expected outcome of 15 percent plus a 5 percent delta; the

EMBOL-X aortic catheter was randomized through Standard J tip cannula; and the primary endpoints again were effectiveness with the demonstration of particulate emboli capture and safety with equivalence of the safety profile using the current standard procedures.

[Slide.]

So this safety endpoint, which might be viewed as also a measure of efficacy, was necessarily not refined enough to demonstrate efficacy based on this sample size. It was mainly used to demonstrate that there would be no increase in problems associated with the instance of death, myocardial infarction, renal insufficiency, GI complications, limb-threatening embolisms, or neurologic deficit, either mild or severe, using the NIH Stroke Scale and other stroke measures.

The safety endpoint was designed to demonstrate freedom from device complications.

Now, it is important to point out that this is mainly a safety endpoint, and for example, the inclusion of myocardial infarction is important to have in a study looking for safety, but we wouldn't aim to actually improve myocardial infarctions, because the device is north of the

heart, as it were.

[Slide.]

The effectiveness endpoint and hypothesis, therefore, was successful capture of the emboli, and this was defined as retrieved particles observed at 10X power at the operating table.

And the hypothesis was that we would capture greater than 75 percent of the cases that would have emboli that was evident.

[Slide.]

The sample size was driven by the safety endpoint--small sample size needed to demonstrate primary effectiveness endpoint of particulate capture, and the 1,286 patients were used to demonstrate safety, and there was a calculation for one interim analysis using a boundary condition under Bryant-Fleming [phonetic] for the Blackwater test.

[Slide.]

Safety was monitored by blinded, independent Clinical Events Adjudication Committees and the independent [inaudible] Monitoring Committee. There was an independent medical monitor. The Core Laboratories were blinded. Randomization was performed just prior to

cannulation in the operating room, and a neurological examiner and the patients themselves were blinded to treatment assignment.

[Slide.]

We had independent EKG Core Laboratories and histological laboratories to evaluate the emboli.

[Slide.]

There was a separate ecocardiographic imaging core laboratory as well for the epi-aortic as well as TEE endpoints.

[Slide.]

And to put this into perspective, as large randomized trials in surgery are difficult to do, this ranks among the top enrolling randomized studies in the history of randomized trials in cardiac surgery. So this was quite an effort to do this well-designed trial in order to demonstrate the endpoints that Dr. Allen will review.

[Slide.]

So if we summarize this, safety was to be demonstrated under an equivalence endpoint in the agreed-upon IDE using a broad net composite safety endpoint chose, which included myocardial infarction, for example. The safety endpoint was

not optimized to demonstrate clinical efficacy or superiority.

Now, there is no question that this could be used if we had a huge sample size to demonstrate some reductions in embolic injury, but we didn't want to fool ourselves by thinking this initially would be the primary viewpoint of this endpoint overall to demonstrate utility.

Therefore, the utility was focused on demonstrating safety first, followed by efficacy to show frequency of actual particulate removal from the operating room.

Now I'll turn it over to Dr. Allen.

DR. ALLEN: Thank you, Madam Chairman and members of the panel.

My name is Keith Allen, and I was a site principal investigator. I practice as a cardiovascular and thoracic surgeon out of Saint Vincent Hospital in Indianapolis.

[Slide.]

From a financial disclosure standpoint, I have no financial interest in the country and certainly no equity investment in the company. I was reimbursed for my travel and time expenses to come today.

[Slide.]

On behalf of the 88 investigators at 22 centers across the U.S. and one Canadian site, I thank the panel for the opportunity to present our clinical results. I think, as you can see from our centers that were utilized in this study, they represent a broad spectrum of cardiac surgery in North America, involving both private, academic, and community centers across the board.

[Slide.]

The inclusion and exclusion criteria are summarized. Obviously, as with any large study like this, particularly when you are looking at safety as an endpoint, there are a number of exclusion criteria to confine your sample size to patients who are going to demonstrate safety for you.

The inclusion criteria were confined to patients who were 60 years and older who either had primary CABG or primary valve procedure.

Some of our exclusion criteria that we feel are important were dialysis dependent, a patient who had a previous stroke who had a residual deficit, or previous surgery or damage to the aorta.

Obviously, the filter has various sizes and is part of the randomization process. To be included in the study, you had to have an internal diameter of the ascending aorta that would appropriately fit a filter that you could put in the patient.

[Slide.]

About 15 percent of patients screened for this study ultimately met inclusion and exclusion criteria, resulting in 1,394 patients available for the study.

As is common with any study of this size and nature in which a new device is being placed in a clinician's hands, we had as a component of our study a roll-in phase. Each investigator was required to do at least one nonrandomized patient to gain familiarity with the device and understand how it could be used and inserted appropriately.

While this does not impact the study results, I will concentrate the rest of our data analysis on patients who were actually randomized between filtered and nonfiltered arms.

We ended up with 1,289 patients who were evenly distributed between filter with standard cannula or simply receiving the standard cannula

alone, without intra-aortic filtration.

It is important to understand our randomization stratification stream, and it really involved three components. Patients were stratified based on whether they were a valve or a primary CABG and, importantly, we randomized patients based on injection fraction.

[Slide.]

There were a number of key baseline and medical variables that were obviously evaluated in this study. There were four variables that differed between groups. One variable that favored a control arm was a patient-given history of aortic disease.

There were three variables--atrial fibrillation, valvular dysfunction and severe carotid disease--which all favored the filter arm. It is important, though, when a multivariable analysis was done on these discrepant variables at the end of the study, there was no interaction or impact on our results.

[Slide.]

It is amazing, as different as cardiac surgeons are across the board how uniformly this operation was done across the centers that were

involved in this study. There was a good distribution between CABG and valve patients. There was a good distribution between whether a partial clamp was used or whether a single-clamp technique was used.

We tried to look at things like whether the aortic cross-clamp was repositioned as an impact on embolic release, and that was similar between arms. Things like cross-clamp time and cardiopulmonary bypass time were also familiar and similar between groups. And, importantly, we wanted to look at nuances like were the number of proximal anastomoses done between groups similar, because obviously, you are manipulating the ascending aorta, and we wanted to ensure that one group wasn't having more proximal anastomoses done than the other. And in fact, they were identical between the two arms.

When we looked at filter dwell time, which obviously is not applicable to the control, the filter dwell time in our patients was approximately 21 minutes.

[Slide.]

As outlined very nicely by Dr. Kuntz our primary composite endpoint was a safety endpoint.

It is important to reemphasize the fact that this was an equivalence safety endpoint, and I think we did achieve that safety endpoint. 17.1 percent of the treatment group compared to 18.9 percent of the control group had a composite event that was a priori defined. And once again, it is a safety endpoint, and it was not intended to capture clinical effectiveness of the device. It is important that the panel understand this and that they don't confuse this safety endpoint as a surrogate for clinical efficacy, because as Dr. Kuntz pointed out, if you were designing a composite endpoint to demonstrate clinical efficacy, you certainly would not have included myocardial infarction which the device can have no impact on and that occurred and represented approximately half of the events in our composite endpoint.

[Slide.]

Any time somebody presents or uses a composite endpoint, as an investigator, I always want to see the details of all the components that were involved in creating that composite endpoint to ensure that there are not trends favoring one or the other that even out when you do just the

composite endpoint.

When you look across-the-board at the components of our composite safety endpoint, we don't make claims of superiority in any area, but what you clearly see is equivalence and safety of the device in a very large prospective randomized trial, not only with the composite endpoint, but with the individual components of that composite endpoint.

[Slide.]

Clearly, in a trial like this where you are presenting people with a major surgical operation, you look at other serious adverse events, and once again, it is striking how evenly distributed these are across centers in this very large study. When you look at serious adverse events across the board, there was no statistical difference between either arm. And when you come down to actually tallying up whether or not patients had a serious adverse event in this very large study, the bottom line down at the bottom is that they were absolutely identical between both the control and the filter group.

[Slide.]

As an investigator who was asked to

participate in this trial, one thing that we were interested in is that obviously, you are placing something inside the ascending aorta. So one of the key adverse events that I was interested in was does placing this device inside the ascending aorta potentially cause harm to the patient. And we captured that using, out of 18 of the 22 centers, sophisticated imaging--primarily epi-aortic scanning, but also transesophageal ecocardiography--to try to capture whether the device was leaving some type of footprint within the ascending aorta.

And we looked at it as both did it cause ascending aortic dissections, and did it have ecocardiographic or imaging abnormalities that we might term aortic wall or intimal changes.

[Slide.]

I think that for the surgeons on the panel, this picture really doesn't need much explanation. As an investigator, this is what I was most concerned about when I was going to put this device in a patient--was I going to cause a clinically significant and relevant aortic dissection?

Clearly, on the left, the blue, engorged

aorta that makes your heart skip as a cardiac surgeon when it occurs is a dreadful complication that has serious clinical implications.

As a surgeon, this is very apparent, and while the TEE is dramatic in showing it, epi-aortic scanning or transesophageal ecocardiography aren't necessary for me to make this diagnosis.

And it is interesting when we look at this serious clinical event, there were two ascending aortic dissections seen in the control arm, and there were no ascending aortic dissections in the EMBOL-X filter arm.

[Slide.]

What we did see was a footprint that may be left by the device. As I told you and as Dr. Kuntz pointed out in his study design, 18 of our 22 centers utilized either epi-aortic scanning or transesophageal ecocardiography peri-procedurally to look at the ascending aorta. And Dr. Weismann at the core lab for ecoocardiography did that very detailed blinded review. And, as will be pointed out later by the FDA, there was an incidence of endothelial disruptions or what I call intimal abnormalities seen more frequently in the filter group compared to the control arm.

What were these endothelial disruptions, and what clinical context can we put them in?

[Slide.]

I think a series of images will hopefully clarify that.

On your left is an epi-aortic scanning of the first endothelial disruption identified very early on in the study by a surgeon. There were three endothelial disruptions that were identified by surgeons early on in the study and that were elected to be repaired. One of those endothelial disruptions was an inadvertent stab from an 11-blade knife to the posterior wall of the ascending aorta. The filter certainly didn't cause that.

But there were two endothelial disruptions, both occurring in the first four months of the study, both at the same center, in which surgeons elected to repair them. There was no historical basis for these. They weren't in the setting of an acute ascending dissection. But the surgeon had no background about what these endothelial disruptions are, and what you see--and it is hard to see unless you turn the lights down and so forth--is this small disruption or intimal

flap that is right there.

The patient had a 0.1-centimeter fibrinous strand removed after the ascending aorta was opened, sent for pathology, closed the ascending aorta, and the patient suffered no sequelae.

DR. EDMUNDS: Could you point out the arch vessel?

DR. ALLEN: This is actually mid-ascending aorta, so it is beyond; the arch vessels wouldn't be seen in this particular vein. It is not scanning farther on down there.

DR. EDMUNDS: That is the pulmonary artery going across.

DR. ALLEN: The pulmonary artery is right here.

[Slide.]

Here is another example. Once again, the surgeon identified this endothelial disruption, and you see it right here. It is a little easier to see it than on the last one. This occurred a little later on in the study after we had experience from the core lab telling us that we were seeing these ultrasound abnormalities, and in this case once again, there was no clinical dissection. The patient was doing fine. And this

surgeon because he had been provided with some of this historical information didn't repair it. And in fact in 10 out of the 13 endothelial disruptions that were identified by surgeons, those surgeons decided not to repair it, and those patients didn't suffer sequelae from it.

DR. TRACY: Before we leave this slide, I think Dr. Edmunds wants some clarification on a couple of things.

DR. EDMUNDS: Can you point out the location or probable location of the deployed filter in relation to these so-called injuries?

DR. ALLEN: I can tell you that we did an analysis on the location of the endothelial disruptions. In both of these cases, the endothelial disruptions were in the mid-ascending aorta. The filter was downstream from these devices, so they weren't in the area of--

DR. EDMUNDS: Where are you cannulating--the sinuses of the falsalva [phonetic]? Where was the cannula, then?

DR. ALLEN: The cannula was approximately right at the innominate [phonetic] artery.

DR. EDMUNDS: So the filter is deployed upstream to the cannula tip?

DR. ALLEN: No, sir.
DR. EDMUNDS: I am totally confused.
DR. ALLEN: The filter is deployed just proximal to the cannulation. It is part of the filtering process of the cannulation itself. It is part of the cannula that goes into the aorta.
DR. EDMUNDS: Yes, but when it is deployed, like a parachute, where is that in relation to the nozzle of the bypass cannula?
DR. ALLEN: It is posterior to it.
DR. EDMUNDS: It is proximal to the aortic cannula spigot?
DR. ALLEN: Yes, and it is distal to the cross-clamp.
DR. TRACY: Maybe at the end, we will review your Slide 6.
DR. ALLEN: I can show you another slide of that.
DR. TRACY: Okay, but let's go ahead with your presentation.
[Slide.]
DR. ALLEN: This is an example of an interoperative photograph that I borrowed from Dr. Banberry [phonetic] at the Cleveland Clinic in a patient who was undergoing a routine aortic valve

replacement in which we hypothesized what these endothelial disruptions might look like based on the one pathologic specimen that was sent and that was resected by a surgeon.

[Slide.]

These are two examples of epi-aortic scans, once again done at Dr. Kouchoukos' center, one involving a filter patient, one involving a control patient. These are based on--we asked the core lab to provide us with representative slides, and once again, without the lights turned down, it is difficult in this patient to see this, but the slight endothelial disruption here, and in a similar area, right here, that are tagged as being what we are calling these intimal injuries or endothelial disruptions.

Once again, these were not identified by the surgeons at the time of the operation even in a center that has a vast experience with this technology and were not repaired by the surgeons and had no clinical sequelae because of that.

[Slide.]

Well, simply telling you that they weren't repaired and that they might not impact things isn't enough for me, and I certainly wouldn't think

it is enough for you. And we asked that we do an analysis on was there a correlation between endothelial disruptions and adverse events.

If you looked at, for example, patients in the filter arm and compared those patients who had EDS with those who didn't have EDS, there certainly was not a correlation with acute adverse composite events.

If you similarly looked at the control patients, and one of the control patients had an endothelial disruption, or nine control patients had endothelial disruptions, and compared those with EDS to those without EDS, there certainly wasn't a correlation with EDS to an adverse event.

And, more importantly, then, if you just forgot whether they were randomized or not and looked at all patients who had EDS and compared adverse composite events to those that didn't have EDS, there clearly is not a correlation to EDS with adverse acute events.

[Slide.]

Are there long-term consequences of EDS? And I think, as part of the presentation, it is important to understand that long-term followup in this study was not part of the protocol. But

surgeons and investigators were interested in that, and we needed to know that what we were doing to our patients wasn't going to hurt them.

So we developed a methodology to try to follow these patients and assess the long-term impact of EDS on composite and individual event rates. As I said, this is not part of the original protocol. But in order to obtain appropriate followup in the image patients, we targeted centers that had the imaging and centers that had EDS; we looked at centers that were high enrollers in order to have less variability between arms, and we also needed to be able to get timely IRB approval for this longer-term followup.

[Slide.]

We ultimately looked at four high-enrolling centers in which 90 percent followup was obtained. We wanted, though, to look specifically at EDS, and obviously, there were some EDSs occurring outside of those four high-enrolling centers. So we wanted to get followup on all EDS, even patients who were roll-in. So we ended up trying to find followup on 58 patients.

Seven patients couldn't have followup. Six of those were simply because we could not get

appropriate IRB approval. We know the patients were alive, but we just couldn't get followup. There was one patient lost to followup.

[Slide.]

We ended up having a 360-day or almost one-year mean followup. And when you looked at composite event rates between filter and control patients out to 360 days mean, there were events occurring, but they were occurring absolutely identical at 6.1 percent between both arms.

[Slide.]

Once again, I asked the question--well, that's great, but I want to know what about the patients who have EDS. And once again, when you look at the filter patients who had EDS compared to those who did not during long-term followup, there was no correlation to an adverse outcome. And when you look at all patients, once again, there wasn't a correlation during long-term followup.

[Slide.]

I come back to the issue of aortic dissections and the development of aneurysms, because while I tell you that long-term followup did not correlate with an acute composite event, what about the development of a late dissection or

the development of an aneurysm.

I told you that in the study, two dissections occurred acutely in the control arm and none in the filter. During followup, no patients were operated on for the development of acute dissections in either arm. There were three additional aneurysms that were seen in control patients--two thoracic aortic aneurysms, one that was repaired, and one abdominal aortic aneurysm that was also repaired. Obviously, none of these were in areas where EDSs were identified, and in fact none of these three patients even had EDS.

[Slide.]

So from a summary standpoint--and I think it is an important safety issue, and that is why we have spent time on this--this was primarily a finding on aortic imaging. Seventy-eight percent of surgeons, despite using sophisticated epi-aortic scanning, were not able to identify these endothelial disruptions. They should not be classified as clinically significant aortic injuries, and while they were seen more frequently in the filter arm, they were seen in both arms.

These are not aortic dissections, and I think our acute data demonstrates no correlation

acutely to composite events, and I think our long-term data and due diligence in collecting that also does not demonstrate a safety issue.

[Slide.]

We had a second primary endpoint which, as Dr. Kuntz pointed out, was an effectiveness endpoint. The hypothesis was that we could capture particulate emboli in greater than 75 percent of the EMBOL-X aortic filters. And in that case, successful emboli capture was defined as retrieved particles observed at 10 times power before histologic processing.

[Slide.]

And I think as these photographs demonstrate, our primary effectiveness endpoint was indeed met. Ninety-six-point-eight percent of filters prior to histologic processing visualized, documented, and photographed captured particles.

[Slide.]

As surgeons, we were interested in what these particles might be composed of, and as part of the trial, we employed a pathologic core lab that would analyze this data.

We anticipated, based on what the core lab was telling us, that because this small amount of

tissue was going to go through extensive histologic processing and handling that there were going to be some specimens lost, displaced or dissolved and not available for analysis. And indeed that is what we found.

We found that approximately 21 percent of previously photographed and visualized specimens were not ultimately available for histologic analysis. However, more than 85 percent of specimens that were available for analysis demonstrated that the material atheromatous in nature.

[Slide.]

There were various other things captured by the filters, and I show as this example RBC thrombus or clot, this polyploid structure in both specimens that, based on its organized nature on pathology, likely came from an intercavitary source, as Dr. Kouchoukos mentioned in his talk.

[Slide.]

It is important that we assure the panel that this device isn't causing what it captures and that it is not thrombogenic. And we did extensive bench-testing to demonstrate that with filters having the 95 percent heparin bonding with a 2-hour

dwell time, they were not thrombogenic. But what about in a human?

[Slide.]

And to assess for thrombogenicity, we used scanning electron microscopy, and it is important to note when the SEM was done.

Unlike the histologic data, which was done obviously after processing, we looked at filters prior to histologic processing. The original intent of the study was to evaluate 10 percent of the filters, but after 5.6 percent of filters had been examined and presented to the FDA, the FDA agreed in a letter on October 12, 2001 that the scanning electron microscopy demonstrated no significant platelet thrombus formation, and we could discontinue doing additional scanning EMs.

[Slide.]

So from a summary standpoint, there certainly were captured particles that were documented and visualized as part of our a priori defined effectiveness endpoint that were not available for histologic analysis. But I contend that they are not available because of the extensive histologic processing that went on and the small amount of material that they represented,

and that scanning electron microscopy does not demonstrate that filters are thrombogenic.

[Slide.]

What about the number of particles captured? I think Dr. Kuntz touched on that by what does it mean whether we capture one particle, five particles, or 20 particles.

The study data demonstrate that there was a mean number of particles captured of 5.6.

[Slide.]

I think it is more interesting to look at the quantity of the particles that were captured, and here, you see a slide looking at the distribution of sizes of particles captured, and we superimposed the previous slide that Dr. Kouchoukos showed you of representative arteries such as middle cerebral artery branch or posterior circulation artery. And we also put in renal interlobular arteries versus the size of renal arcuate arteries, or intralobular renal arteries.

And you see that the vast majority of the size of the particles that we captured are filtered or would be filtered by small arcuate or cortical cerebral arteries.

[Slide.]

So from a clinical study overview, we feel that we have met both of our primary endpoints successfully--that effectiveness was demonstrated in that 96.8 percent of filters did capture emboli as documented under 10 times magnification; and we certainly feel that our safety endpoint of equivalence was met and that no clinical adverse events were associated with the findings of epi-aortic scanning.

I think I reemphasized the point that our study was not powered nor was it designed to demonstrate superiority in this low-risk patient which was specifically selected to demonstrate safety.

[Slide.]

Following the completion of the study, the FDA, because this was a safety equivalency study, asked the company as well as the investigators whether study data could be extrapolated to clinical efficacy, and this was one of the questions that they had actually posed to the panel.

And I think it is important that we in an attempt to answer this question did some additional analysis. But this additional analysis is in no

way claims for labeling, and we don't make claims of superiority. It is simply an attempt to answer those questions raised by the FDA.

From a surgeon's standpoint, we know that clinical outcomes are influenced by preoperative risk variables, so we felt that if you looked at the high-risk patients in our population, could we extrapolate some clinical benefit or efficacy.

[Slide.]

We utilized the Cleveland Clinic score, as published by Dr. Higgins in JAMA in 1992, to assess for preoperative risk. We specifically chose the Cleveland Clinic score because it looks at both morbidity and mortality unlike, for example, the STS or the New York State Index, which only look at mortality.

The Cleveland Clinic score which is utilized at our center is a validated preoperative risk score that has been validated in over 9,000 patients, and a score of 5 or higher has been validated for increased morbidity and mortality.

Eighteen-point-seven percent of the 1,289 patients randomized in this study met the criteria for moderate to high risk.

[Slide.]

When we looked at whether high- or low-risk patients had composite events, you will see that when we control filter to control in low-risk patients, a Cleveland Clinic score of zero to 4, there was absolutely no difference between the two groups.

But when we looked at patients who had Cleveland Clinic scores greater than 5 as defined in that Higgins paper, we saw that the trend certainly favored statistically patients who received the filter.

[Slide.]

When we looked at components of that composite event and compared those to patients who had Cleveland Clinic scores greater than 5, across a broad range of all unselected components of the composite endpoints, there weren't statistical differences between groups except for renal insufficiency.

I think it is important that we break it out as dialysis patients, patients without dialysis, or all patients who had renal insufficiency as defined in our study. And when you look at all patients with renal insufficiency, it was significantly less in the filter patients.

[Slide.]

Now, renal insufficiency is not as sexy and glamorous as preventing frank stroke, but I think renal insufficiency has a significant clinical impact. We know that based on the STS data base, renal insufficiency is a predictor of increased morbidity and mortality postoperatively, but when you look at patients who had renal events, their length of stay was a little under 15 days. For those patients who did not have renal insufficiency in this study, their length of stay was 7.2 days.

And this looks at all patients with renal insufficiency. The data isn't simply driven by those who had dialysis. If you take out the dialysis patients, which you would expect to have an even longer length of stay, the length of stay only drops by one day.

[Slide.]

I think this slide has put it in perspective for a lot of the investigators in the study, because it helps us evaluate the risk-benefit of this device. It is an odds ratio comparison of baseline variables that, as surgeons, we know are predictive of increased postoperative

morbidity and mortality.

You can see the middle line demonstrating no benefit one way or the other; to the left, the filter arm tends to do better; to the right, the control patients tend to do better.

Once again, we don't make claims of superiority, but it is interesting when you look at this odds ratio table that the vast majority of events are mitigated by placement of a filter.

[Slide.]

This additional analysis to address the possible clinical efficacy I think does demonstrate that at least in moderate- to high-risk patients, there may be a benefit--and I underline "may." Captured particles were predominantly of the size associated with cerebral and renal cortical arteries. The reduction in renal insufficiency events can be demonstrated with a sensitive marker in those high-risk patients. But the study was not designed to assess for neurocognitive dysfunction, and we make no claims for that.

[Slide.]

In summary, our study objective was to demonstrate that particular captured could be safely accomplished in lower-risk populations

against the backdrop of known detrimental effects of particulate emboli.

The risks of this device I think have been safely assured by the equivalency of our composite safety endpoint. Across this large prospective study, serious adverse events were identical between groups.

Certainly, using epi-aortic imaging, we did demonstrate an increased incidence of these endothelial or intimal disruptions, but I think that certainly there was no acute correlation to adverse events, and our due diligence to try to provide you with some long-term clinical followup hopefully provides that there is not a correlation with long-term events.

The benefits of this are that particulate capture was clearly demonstrated in 97 percent of filters, and we feel that the additional analysis asked for by the FDA does demonstrate that clinical efficacy can be reasonably extrapolated from particulate capture.

MS. CHANG: I would like to thank Dr. Allen, Kouchoukos, and Dr. Kuntz for the presentation today.

We believe that the study design and

clinical [inaudible] supports the following indications for the study, and, Dr. Edmunds, if you would like me to answer your earlier question, I can do that for you, as to location of the epi-aortic imaging.

DR. EDMUNDS: I think you have done that.

MS. CHANG: Okay.

DR. EDMUNDS: I have to say I missed it--it was in the writeup, but your diagram was a little misleading, or at least I didn't interpret it right.

MS. CHANG: Sorry.

Questions and Answers

DR. TRACY: Okay. I would like to ask the panel if they have any brief clarifying questions for the sponsor at this time. This is not the open committee discussion, but just clarifying questions.

Yes?

DR. MARLER: I was interested in the details of the discussion that led to the conclusion that there were not cognitive outcomes that could be used, and who participated.

DR. KUNTZ: In the discussion with whom? With the FDA?

DR. MARLER: You mentioned that you reached the conclusion that there was no outcome that could be agreed upon, and I was just wanting to hear some more details about that and who couldn't agree.

DR. KUNTZ: All right. I may refer this to [inaudible] who is an expert in this area, but we reviewed--I think the Stump [phonetic] battery of criteria at that time, which I think was probably the best candidate overall, but they were a collection of approximately 6 to 12 instruments and batteries, and at that time, we didn't think there was a consensus or a study that had demonstrated or validated that those outcomes could be correlated with changes in cognitive dysfunction in 1999, and we were not aware of any validations of that emerging battery of tests, which I think is being refined and is probably a good set, but at that time, it was difficult to say if there was consensus.

Maybe I could call up two other people who may want to make some comments.

Dr. Gold?

DR. GOLD: Thank you.

My name is Jeff Gold, and I am a cardiac

surgeon from New York, and I do indeed own some stock options in EMBOL-X and have been involved in a study of neurologic and cognitive function associated with cardiac surgery for perhaps longer than I care to remember sometimes.

The definition of cognitive changes associated with cardiac surgery has bee a complex and moving target for an extremely long time. There have been, as I am sure you are all aware, at least one consensus panel and several others looking at development of a battery of tests.

However, at the time that this study was conceived, not only was there not a defined battery of tests that cardiac surgeons across the board could agree upon, let alone psychometricians and neurologists, but the etiology of cognitive abnormalities was also highly controversial at the time.

You might recall a very interesting study published by a Dr. Rousseau, who looked at the incidence of cognitive function abnormalities in patients undergoing total knee replacement surgery under local anesthesia. The incidence of cognitive abnormalities in that 524-patient cohort was exactly equal to an equivalent study done in

patients undergoing coronary bypass surgery.
So perhaps the art has improved. Perhaps if we were to redo this at a time in the future, we could agree upon a panel of tests. But if you were to ask about the significance of cognitive abnormalities among practicing cardiac surgeons today, and our ability to reliably demonstrate them, I would say they are poor.
DR. TRACY: Dr. Aziz?
DR. AZIZ: From what I understand, the way that you place this catheter, this could not protect against the sandblast effect of emboli being dispersed; is that right?
DR. ALLEN: Yes, sir.
DR. AZIZ: Okay. And secondly, so this cannula has to be inserted proximal to the enormid [phonetic] artery; is that right?
DR. ALLEN: The cannula is inserted identically. There is no difference in what you do. If you were to, for example, cannulate the arch, as we sometimes have to, yes, you wouldn't use this cannula in somebody, for example, that you were going to cannulate the mid-arch.
DR. TRACY: Dr. Laskey?
DR. LASKEY: Dr. Allen, these

ECO-abnormalities detected in the core lab, I am assume that there are pre-/post-placement ECOs. is this a serial analysis where the ecocardiogram is obtained only at one time, or was there some protocol that people adhered to where you had baseline ECOs and then ECOs during place and ECOs after placement? How was that done?

DR. ALLEN: That's a very good question. It was quite laborious to do this. Actually, our center did not do imaging. I will let Dr. Kouchoukos' center answer that, because his study was actually doing epi-aortic scanning.

DR. KOUCHOUKOS: The epi-aortic scanning was performed after the pericardium was opened, before instituting cardiopulmonary bypass, and at the completion of the procedure, after removal of all the cannulas, administration of protamine, another scan was performed in the longitudinal and transverse planes for the whole ascending aorta.

DR. EDMUNDS: Nick, could you explain how this was deployed? You say you didn't leave the filter up for 60 minutes, and you deployed it when you first started to manipulate and got the cannula in so you could deploy it.

DR. KOUCHOUKOS: Yes. The cannula was

deployed immediately before removal of the aortic cross-clamp--in other words, after completion of the proximal and distal anastomosis and the bypass operation or closure of the aorta or the left mitral valve replacement--

DR. EDMUNDS: It was removed.

DR. KOUCHOUKOS: --it was removed. And then it was left in place generally until the protamine was administered. And the safety analyses indicate it could be left for an hour, but it was left on average for 20 minutes.

DR. EDMUNDS: So you put the aortic cross-clamp on without the filter deployed?

DR. KOUCHOUKOS: That's correct. The filter was deployed into the aortic cannula immediately before removal of the cross-clamp.

DR. EDMUNDS: So you are not claiming that you got all the emboli; you just got what you got.

DR. KOUCHOUKOS: Well, based on the analyses that I presented, the majority of these emboli are released at the time of removal of the cross-clamp, and that was the logic for deploying the filter immediately before release of the clamp.

DR. EDMUNDS: Well, you did the studies, but on Dick Clark's study, I thought you got a

shower of emboli when you put the clamp on, also; is that not correct?

DR. KOUCHOUKOS: Well, I think I showed you a slide showing that there are emboli released at various times during the course of a cardiac surgical procedure, but that the majority of the emboli are released at the time of release of the cross-clamp.

DR. EDMUNDS: Oh, I agree with that, yes.

DR. TRACY: Okay. Are there any other clarifying questions? We'll have the open committee discussion in a few minutes after the FDA presentation, but are there any other clarifying questions?

DR. KRUCOFF: Just a pluming question. Relative to, say, any other commercial cannula that you would use routinely, is this cannula different from a flexibility or a dimensional perspective?

MS. CHANG: Let me show a picture of the product again.

[Slide.]

MS. CHANG: Actually, this main body is what a standard cannula looks like, and we have modified it so that we have added a sideport there. There is still only one hole, so it is actually

virtually identical to existing commercial cannulas. So the big difference is the sideport.

DR. KRUCOFF: Okay. So my question is does the presence of the sideport affect in any way the portion of the cannula that actually goes through the aorta relative to a commercial, in either dimension, or just how it feels?

DR. ALLEN: The short answer is "No," and I think Dr. Kouchoukos would concur with that.

DR. TRACY: Okay. One more question.

DR. DeMETS: I would like to ask what about the randomization process. You didn't describe it in your presentation, but your writeup, as I understand it, there were some patients who did not get treated as randomized.

Could you walk me through that process so I can understand exactly what happened and what you did about it?

DR. ALLEN: The specific details--the patient was obviously net inclusion and exclusion criteria. The one exclusion criterion that couldn't be determined until you actually got in the operating room was whether his ascending aorta was of an appropriate size. So the patient had a stronotomy [phonetic], and then you measured the

ascending aorta approximately 1.5 centimeters below the nominid [phonetic] artery, which is about where the filter would be deployed, and if it fell into an appropriate range, then a randomization card was opened, and the patient then was either randomized to have a standard J-tip cannula or a modified J-tip cannula inserted.

There were nine patients who, when the card was opened early on in the study, the way the card read at the top was "The EMBOL-X Study," and actually, the very first patient that I randomized, our coordinators read the patient was in the EMBOL-X study, and they assumed he was a filter patient when indeed, you had to read the line below it, which said whether he was a control or a filter patient.

Those happened very early on in the study, and once they were educated about it, they ceased to happen. And in fact, in three of those nine, we actually caught the mistake before we actually put one device or the other in.

Does that clarify that for you?

DR. DeMETS: That clarifies the first part. The second part is given that that happened, which I now understand how it happened, in which

group were the patients left?
DR. ALLEN: Intent to treat.
DR. DeMETS: So they were left in the group that they should have been randomized to?
DR. ALLEN: Correct. And they represent a very small proportion of the number of patients that we put in the study, but we did an intent to treat analysis.
DR. DeMETS: Thank you.
DR. TRACY: Dr. Ferguson?
DR. FERGUSON: I missed one point about the cannula. I thought from my reading that you used the cannula with the sideport even in the control group. That is not the case?
DR. ALLEN: No. The standard cannula is the cannula that I trained with in Chicago, which is just a standard J-tip cannula. So essentially, if you take the--
DR. FERGUSON: Is that a cannula manufactured by this company?
DR. ALLEN: No. That's a standard J-tip cannula.
DR. FERGUSON: Did everybody use--
DR. ALLEN: Everybody.
DR. FERGUSON: --were they instructed to

use that same cannula?
DR. ALLEN: Yes. Everybody used the same cannula. So all control patients, regardless of what your standard cannula was at your site, you had to use the same standardized cannula.
DR. FERGUSON: And I would ask again, if I may, when the standard cannula and then this cannula are affixed to the aorta, the aortic size and so forth at that point of entry into the aorta are both the same size?
DR. ALLEN: It is identical. The only part that is inside the ascending aorta is right there.
DR. FERGUSON: I understand that, but I just want to be sure that the impact of the sidebar does not enlarge that--
DR. ALLEN: No, sir, it doesn't. That's a great question, but no, sir, it doesn't.
DR. TRACY: Mr. Morton?
MR. MORTON: Madam Chair, does the sponsor have an example available, and would you mind if the panel could see it?
DR. TRACY: No. Are we allowed to do that?
DR. ZUCKERMAN: Yes. We can take a look

at an example.
DR. TRACY: Okay. Do you have that available?
DR. ALLEN: [Handing.] I'll give it to the cardiac surgeons first.
[Laughter.]
DR. EDMUNDS: Can I ask a question? Is there any connection between the flow path from the pump and the deployment path of this filter?
DR. ALLEN: If I'm understanding you--
DR. EDMUNDS: In other words, this sort of filter deployment apparatus is just riding shotgun on the cannula. There is really no hole between the two.
DR. ALLEN: Yes.
DR. EDMUNDS: You vent the air out by blood coming around the wire that is around the filter.
DR. ALLEN: Actually, that's a great question, and it involves a safety issue with how the air is vented.
The filter--I don't know if we actually have a filter to show you--there is a plug, much like is on the standard cannula, which allows air to be vented. So when you put the filter in, you

see the white plug turn red, indicating that blood has come up and evacuated in the air. And obviously, if you don't see that, you need to change filters or do something differently.

DR. MARLER: I had a question on page 68, Tables 7-18 and 7-19--and I'm sure there is an explanation, but I just didn't understand why there were adverse events, NIH Stroke Scale greater than 4, 13 in the control group, with 644 patients--

DR. TRACY: I think this may actually be more appropriate for the open committee discussion. Unless there are some very brief clarification questions, I'd like to stop at this point for a break.

DR. EDMUNDS: Where does the damn thing come out? Does it come out this hole or some other hole?

[Dr. Allen handing sample to Dr. Edmunds.]

DR. EDMUNDS: Why don't you show everybody, because I can't be the only one confused.

DR. ALLEN: The cannula is inserted as you would any other cannula; the cannulation is no different. Once the cannula is inserted, patients are put on cardiopulmonary bypass, everything is

done--you manipulate the heart, you do your proximals, you do your distals, and so forth. Just before you release the cross-clamp, you take out this plug, and you insert the filter, and the filter goes in like this.

The air venting that you alluded to, for those of you--and I will pass this around--there is a white hemostatic pump that allows fluid to vent out and push the air out just like our cannulas do today. Once you confirm that it is vented appropriately, the device is deployed, just like this.

DR. EDMUNDS: Why don't you pass that around?

DR. ALLEN: And then the cross-clamp is released.

DR. TRACY: While that thing is making its way around--Dr. Aziz?

DR. AZIZ: So during the time that you take the stop off to put the actual filter in, could air get in, or is there a one-way valve that is--

DR. ALLEN: No. It's one-way. It is a one-way valve.

DR. TRACY: Okay. I think at this point,

while that is working its way around, we'll take a 15-minute break and resume at approximately 20 of 11.

DR. ALLEN: Thank you.

[Break.]

DR. TRACY: I'd like to reconvene the meeting at this point and ask the FDA to begin their presentation.

FDA Presentation

MS. WENTZ: Good morning. My name is Catherine Wentz, and I'll be opening up the FDA presentation for the EMBOL-X aortic filter.

This will be done in four parts. I will do an introduction. Dr. Julie Swain will follow up with her clinical summary. Dr. Gerry Gray will then do his statistical summary, and I will then close with the questions to the panel.

[Slide.]

I'll start with a brief description. EMBOL-X gave you a better one than I can, but this is just a short reiteration.

The EMBOL-X aortic filter is used in conjunction with the EMBOL-X aortic cannula which was cleared this past September and is "intended to contain and remove particulate emboli from the

ascending aorta during and following cross-clamp removal and as the heart resumes ejection."

The heparin-coated filter has a pore size of 120 microns and is mounted on a nitinol frame. The filter is inserted into the ascending aorta via a sideport on the EMBOL-X cannula. The flexible wire filter frame expands upon insertion into the vessel and is available in five sizes. The filter is then retracted back through the same sideport at the end of the procedure.

[Slide.]

In the next three slides, I would just like to reiterate briefly some regulatory information that I think you all received in your training this morning.

I would also like to reiterate that this is just for your information and should not enter into the discussion of the EMBOL-X study. It will be FDA's responsibility to take the recommendations made today at the panel meeting to make a final decision within the 510(k) realm.

So just to reiterate some definitions, the 510(k) requires a manufacturer to demonstrate substantial equivalence or SE to a legally marketed predicate device.

To further define substantial equivalence, substantial equivalence basically means that the two devices have the same intended use, similar technology, and if the technology is not similar, there are means by which to demonstrate that the new technology does not affect equivalent performance or the risk profile.

[Slide.]

A PMA is defined as a process where the FDA evaluates Class III medical devices. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health or which present a potential unreasonable risk of illness or injury.

[Slide.]

Now, to put this submission into that context, the EMBOL-X aortic filter originally underwent a clinical study to demonstrate the safety and effectiveness of the device in support of a PMA application.

However, in June of 2001, the PercuSurge device, which is also an embolic protection device, was cleared through the 510(k) regulatory pathway opening the doors for the EMBOL-X aortic filter to

be reviewed under the 510(k) regulations.

The PercuSurge device, which has a similar intended use to EMBOL-X, in conjunction with cardiopulmonary bypass arterial line blood filters, which has similar technology to the EMBOL-X device, will be used as a combination predicate for the EMBOL-X device in the determination of substantial equivalence under the 510(k) regulations.

[Slide.]

To go over a little bit of the history of how the endpoints for this study were developed, at the beginning, the sponsor wanted a nonclinical effectiveness endpoint--that is, to capture debris--and an equivalence safety study. The FDA consistently expressed concerns regarding the interpretability of the proposed endpoints.

FDA, however, agreed to the proposed effectiveness endpoint assuming that the safety endpoint, which included some neurologic outcomes and other embolic-related events, would capture the clinical effectiveness of the device; and that the device labeling would be restricted to only the facts from the study. No clinical implications could be made from the capture of debris since none was evaluated.

[Slide.]

And briefly, just one slide of engineering--that is my background; I performed the engineering review of the submission.

Overall, on the bench studies, there were some design concerns and/or test method concerns that remain that may be related to the endothelial injuries observed with this device. These concerns are presently being addressed.

Both the biocompatibility and sterilization, packaging, and shelf-life had no further questions; they were all fine.

I think this is the point where I turn it over to Julie for her clinical review.

DR. SWAIN: Thank you for the opportunity to present.

Let me make a comment first, that I am at somewhat of a disadvantage in that we traditionally exchange presentations with the sponsors before the talk so we can mold our presentations, and we provided our slides to the sponsor, and the sponsor chose not to provide theirs, so I think that some of the comments that I will make are a little bit off-the-cuff in response to some of the presentations that I had no knowledge that these

items were going to be presented.

[Slide.]

The clinical review was done by both Wolf Sapirstein and myself, and we are both cardiothoracic surgeons. I am a consultant to the FDA.

[Slide.]

The study design, as you have seen, was randomized, which is important in I think one of the discussions that we will have about the neuropsych--it is a randomized, multicenter trial and one of the largest trials done--control arm, patients without filter; and an interim data analysis was planned at 50 percent of the patients.

[Slide.]

In the study plan, it was said that "If the hypothesis tests performed at the interim are statistically significant, indicating emboli capture and equivalent safety, the study will be terminated."

However, the study was continued with the attempt to show safety superiority, and that is some of the data that we will discuss.

[Slide.]

Inclusion/exclusion criteria are patients

with elective operations; isolated coronary bypass or valve; greater than age 60; and there were a total of 24 exclusion criteria. One was neurological deficit; one was a history of major stroke as defined by the clinical history of a fixed, focal neurological deficit attributable to stroke; redo operations; and renal failure on dialysis.

[Slide.]

Neurological evaluation was essentially gross neurologic testing--history, physical exam; NIH stroke score; and no neuropsychological testing. And I have to say that I disagree with some of the comments made. Dr. Kuntz was talking about reviewing this 3 years. I have spent probably a quarter of a century as my major interest in the neurological effects on cardiac surgery, and the consensus conference, the Key West Conference in 1995, published in the Annals of Thoracic Surgery when Dr. Ferguson was the editor, and then the updates published when Dr. Edmunds is now the editor, listed the problems and the suggestions of the tests that could be done. And the comment was made that cardiac surgeons now still don't agree.

There was a very nice conference about 5 months ago, sponsored by the NIH, where the leaders in the field were invited to discuss this problem. I attended the conference, and we essentially had subgroups, and the subgroup that I was in was a neuropsych group--I don't believe anyone else in this room that I recognize was at that conference in that particular area--and I disagree that there were no neuropsychological tests 3 years ago and that there is none now.

And again, this is a randomized study, so we know that a lot of things cause changes after cardiac surgery or knee operations or whatever--but that's the beauty of a randomized study, that one can then look at the changes.

And when you look at a device that perhaps you have difficulty showing efficacy, it may be that it is not efficacious or that you didn't measure the most sensitive measures. And that may be relevant to the discussion here.

[Slide.]

What are the endpoints? Efficacy is that greater than 75 percent of the filters would capture at least one particle. And there was a composite primary safety endpoint composing several

items, essentially saying that it wouldn't be worse than normal cardiac surgery, more than 5 percent worse.

One of the secondary safeties was aortic injury, which was not really part of the composite safety primary endpoint.

[Slide.]

On patient demographics, there are really no statistical differences in the baseline. It was a well-randomized study. The treatment group was 73 percent male, 91 percent Caucasian, an average age of 71, and 84 percent of patients had an isolated coronary bypass operation.

[Slide.]

The composite safety endpoint comprised the items that are seen here. Renal were an elevation of creatinine, and then, a new dialysis requirement. Neurological divided into stroke, TIAs, nonmetabolics. Cardiac is Q-wave MI and non-Q-wave MI.

[Slide.]

We looked at the number of particles trapped, and the average was, I believe, 5.6 mean particles per filter. The problem is--a denominator has been mentioned by the panel

members--you don't know how many particles are liberated--there was no middle cerebral doppler or carotid measurements made, and that probably wouldn't help a lot.

We also know that particulate matter and gaseous emboli are the two main causes of neurological dysfunction. This does nothing to gaseous; we are talking about particulate, as Dr. Kouchoukos said.

[Slide.]

When you look at the maximum number trapped in some filters, it was 25 in the regular study and 38 in the roll-in patients, so maybe that gives you an idea of what the denominator is, because you would love to know the percentage of particles trapped, but you really can't know that information. That may also have an influence on the efficacy of this device or the clinical utility.

[Slide.]

I picked out just selected events--in neurological, I picked out stroke; in renal failure, I picked out dialysis; in MIs, I picked out Q-wave MIs. And I think as the comment was made yesterday by Dr. Kuntz, you like to see a trend of

everything in the same direction, and you really don't see a lot of trends here in these events.

Now, the comment was made by two of the three speakers, and certainly not Dr. Kouchoukos, that MI is irrelevant here. Well, it is highly relevant--it is actually the first adverse event that I would think of.

When you have that--I don't know where that device is--but the filter is between the outflow cannula and the aortic cross-clamp. Well, we all know that you get retrograde flow in the aorta. You get it in many instances; that's how we close aortic valves and get aortic insufficiency--but in cardiac surgery, when you take an aortic cross-clamp off, you've got an essentially normally pressured aorta, or we drop the pressure transiently, and you've got very often a sucked-on aorta that has collapsed with very minimal pressure, so you always get retrograde flow.

So I would look at myocardial infarction as a physiologist as being one of the more interesting adverse events in this. And then, the first branch of the aorta is the coronary artery, the second branch is the neuro-feeding vessels. So

those are the areas that I tend to be most concerned with.

[Slide.]

We looked at--I use the term "manipulation-related aortic injury." It is used in the literature, and in fact it is used in the literature quoted by the sponsor. So when you look at manipulation-related aortic injury, we can see that there are changes, and we really don't know what this means, as the sponsor pointed out.

In this acute study, the patients were followed an average--a median followup was 7.0 days--it was during their hospitalization--and what that implies to whether you find an injury.

This occurred in 9.2 percent of the filter patients--42--in the regular study. Three of the filter patients, as has been said, required aortic repair. I know that the dissection ones that the control group had were the only ones placed up there in the table. However, three of the patients, the surgeons did choose to do an aortic repair, which is a fairly major procedure to add onto an isolated coronary bypass. Whether that was a correct decision or not, it is the data.

[Slide.]

The study protocol showed 30-day followup or hospital discharge, whichever occurred first; so the median was 7.0 days to study these patients.

And then there is the post hoc study that was a telephone followup that followed up 43 of the 49 aortic injury patients and 18 of them were followed for greater than one year by telephone followup.

So I think it was a good effort by the sponsor to see if you could find in this type of study whether there were adverse events, and again, none was found. Also, there was no apparent training effect in that you didn't get more of these at the beginning. They were pretty evenly distributed throughout the study.

And again, they were not associated with the adverse events that were measured in this study.

[Slide.]

When we looked at the post hoc data analysis--I was not present at the FDA when this was discussed, but I don't think that the exact type of analysis was specified--in fact, I know it wasn't. The problem of a post hoc data analysis is that they are not planned actively in the

investigational plan, so the statistical treatment that Dr. Gray will talk about is somewhat difficult in that a .05 P value is probably not the P value that would be interesting for you. And nominal P values do not account for multiplicity; you can do multiple analyses and find something that has a P value. And there is really no way to know how much adjustment should be applied when judging the significance of this.

[Slide.]

We looked at Higgins score, and Higgins score was chosen because it is generally used at one institution; it is a lot less used than some of the more common, SDS database or New York Heart, and although those two don't look at adverse events so much, they really do tell you how sick a patient you have, because it is an estimation of mortality.

I have spent 24 years with the STS database, and I think that that is probably an interesting way to look at the data, and we don't have the results of that analysis.

However, when we look at the Higgins score greater than 5, again you can see that when you look at death, slightly favored in the filter group, and stroke, slightly favored in the control

group, there is really no consistent trend in these data.

[Slide.]

So in summary, the filter trapped at least one particle in 97 percent of the cases. The composite safety endpoints were really not different between the two, as the hypothesis was. The individual safety events, there were no significant differences; and the only difference was in the manipulation-related aortic injury.

[Slide.]

Conclusions: The filter traps particles; a correlation with clinical improvement was not shown; there were additional concerns raised by the occurrence of aortic injuries.

Thank you.

DR. GRAY: Good morning. My name is Gerry Gray, and I was the statistical reviewer for this submission.

[Slide.]

I am going to just address a few issues. First, I am going to talk a little bit about judging the results of the trial, because I think that's really the crux of any kind of disagreement we might have with this trial.

Next, I'm going to talk a bit about particulate capture as a surrogate endpoint; and finally, I will finish up with the subgroup analyses and the Higgins risk scores.

[Slide.]

The first issue is how are we going to judge the results of the trial, and of course, the bottom line is always the tradeoff between a probable benefit and a potential risk. I would say that both of those things are kind of hazy in this case.

And the other thing you have to think about is what the appropriate set of endpoints to be using, and what is the appropriate control/comparator group.

[Slide.]

So, really, in this case, there are three main ways that you might judge the results. The first one being the most compelling is that the results are judged internally to the study, with clinical outcomes compared to a control group in a randomized trial, and at that level, you can really make pretty sound causal inferences.

The next level might be to judge the results in comparison to other similar devices

and/or studies that you might have.

And the third way that you might think about it is judging the results narrowly, based purely on proposed claims, thinking of the device as a "tool," in effect, and comparing that to some predefined criteria you might have for effectiveness of that tool. And in this scenario, really, there is no demonstration of clinical effectiveness.

[Slide.]

So, internally, using the adverse event composite as the endpoint, again, we had 1,289 patients randomized to the EMBOL-X versus control, the outcome being the major composite adverse event rate. We had 17.1 percent of events in the EMBOL-X arm and 18.9 percent in the control.

The first statistical test is for noninferiority, and that was with an equivalence delta of 5 percent. So in other words, we are testing whether the EMBOL-X is no more than 5 percent worse than the control. And that is strongly rejected, so that certainly we can say that the EMBOL-X device is equivalent to the control if you measure that as 5 percent.

And contrary to what I heard in the

sponsor's presentation, there as an amendment to the IDE that specified that we would do another test for superiority for this adverse event composite, and you can do that without any worries about alpha penalty, but that test is not at all significant; the P value is 0.38.

So the bottom line is, as you have probably already come to a similar conclusion, for the adverse event rates, the devices are equivalent but not superior in terms of this endpoint.

[Slide.]

Internally to the study, using the endpoint of particulate capture, the outcome is the proportion of the filters that capture at least one particle. And for this endpoint, there is no way to judge internally, because there was no comparison group that we had.

[Slide.]

For the other safety endpoint, to me, it looks like the results for safety are actually remarkably similar. Of all the types of serious adverse events, all 32 that we saw that the sponsor presented in one of their tables, there was none that came even close to being significant in either direction.

So for all the other safety endpoints, there is no evidence of any difference between the device arm and the control arm.

And finally, there was a secondary endpoint, as has been discussed, on aortic endothelial injury that was significantly higher in the EMBOL-X arm, but again, there is no detectable effect or outcome from those aortic injuries on any clinical adverse events. For short-term followup, there were 42 randomized patients.

[Slide.]

You might think you could compare the results of this study to some other device or a similar device. The predicate for the EMBOL-X device is the PercuSurge balloon aspiration catheter for SVG patients combined with the meshes in the CPB arterial filters.

Unfortunately, though, the two devices are really fairly different in terms of their mechanism action, and they are fairly different in terms of the patient populations that were studied.

So really, from my point of view, this is sort of a dead end; you can't really make a comparison with this device.

[Slide.]

Finally, based on the proposed claims, the evaluation of the device as a tool, the claim says "to contain and remove particulate emboli," and certainly the device is successful in that regard because it was successfully deployed in about 96 percent of the patients, and depending on the denominator that you use--either the number of filters or the number of patients--it captured one or more particle in either 97 or 92.5 percent of the time.

So that easily meets the predefined criteria of particulate capture in 75 percent of the filtered patients.

[Slide.]

So to summarize, the internal evidence is for equivalent safety, and there is no evidence of any effect on adverse event rates.

Externally, it is very difficult to make any comparison, and as a tool, the device certainly captures particulate material, and from the sponsor's summary slide, they said "Clinical efficacy can be reasonably extrapolated." So if you choose that route, you may get extrapolation.

[Slide.]

Let me just talk a little bit about

particular capture as a surrogate, because one way you might justify the particulate capture is to think it is a surrogate for some clinically meaningful endpoint. And the question here in bullet number two--is particulate capture, however you measure that, a valid surrogate for clinical adverse events?

Really, to be a valid surrogate, the endpoint has to be somehow correlated with the outcome of interest, and somehow it has to capture the effect of the treatment on that outcome.

[Slide.]

So just going down that path a little bit, here is a two-by-two table that shows whether or not particles were captured and then whether or not a composite event was observed. And as you can see, the correlation coefficient is quite small there. There is really no obvious correlation that I can see between particulate capture and whether or not there was a composite event.

It is the same if you do number of particles captured, whether it captured any particle or not, or if you measured the total surface area of particles captured.

[Slide.]

Looking at that a little further, this is called an Q-Q [phonetic] plot, and it plots the quantiles of two distributions.

Here, on the X axis is the number of particles captured in patients who had no composite event, and the Y axis shows the number of particles captured in patients who did have a composite event. And if the two distributions are the same, we would expect that to be a straight 45-degree lines, and indeed, it is almost entirely a straight 45-degree line. So there is no real evidence that there is any difference, except potentially out in the fair tail there, where you have more than 12 or 15 particles captured.countries

[Slide.]

So I did a little bit of--well, actually, first of all, here is the same kind of plot that is using particle area instead of number of particles, and it looks the same, visually.

The only thing that would make you think there might be a relationship would e what is going on in the extreme tails here, where you have more than 10, 12, 15 particles captured. So I did a little bit of data-dredging of my own to try to figure out if there was anything going on out

there, and that represents about 46 patients, I think it was, out of the 1,200 in the trial. It is relatively low numbers, and from a statistical point of view, you can't really draw any conclusions from those.

[Slide.]

So in regard to particulate capture as a surrogate, it really doesn't meet the condition that it is correlated with the outcome of interest.

And similar results hold if you use other endpoints, or other kinds of adverse events not included in the composite.

It is possible, of course, as Rick Kuntz pointed out, that there could be effects that are so subtle that they were not measured in this trial, and therefore, we have no way of knowing whether there is any effect on them.

[Slide.]

The third and final topic is just covering the basis on the subgroup analyses. The sponsor acknowledged this, that on Table 6 of their panel package, they have 36 different subgroup analyses that they performed, and certainly, when you look at them through the statistical viewpoint, the P values are small, but given the number of subgroups

that we have gone through, that really is not surprising at all.

[Slide.]

And finally, for the preoperative Higgins risk score, really, that is in a sense another subgroup analysis, because we have used the Higgins risk--we tried several cuts on the Higgins risk score and found one where the P value was slightly less than .05. But in order to make any strong statistical conclusion from that, we would need to know how small the P value has to be to be significant, and .047 really isn't it if you do any reasonable adjustment for multiplicity.

[Slide.]

So to summarize the last subject, the subgroup analyses really don't provide any evidence of superiority in terms of adverse event rates. And again, I heard this pretty clearly from the sponsor's presentation as well.

That concludes my presentation.

MS. WENTZ: Thanks very much.

At this point, I just want to review the Questions to the Panel, and I believe there are six.

Question 1. The primary safety endpoint

for this study was a composite of seven clinical adverse events including death, neurologic deficit mild and severe, renal insufficiency, perioperative myocardial infarction, gastrointestinal complications, and limb-threatening peripheral embolism, evaluated at hospital discharge or 30 days, whichever was shorter. The median followup time was seven days.

Some facts from the study are: The observed overall composite event rates were 17.1 percent in the EMBOL-X arm and 18.9 percent in the control.

The composite event rate for the EMBOL-X arm was shown to be equivalent--not more than 5 percent higher--than the control.

Also as specified in the protocol, a separate test for a lower event rate in the EMBOL-X arm was not statistically significant.

The EMBOL-X arm demonstrated a significantly higher incidence of aortic endothelial injury--9.2 percent versus 2.0 percent. Although these patients did not appear to have any short-term clinical sequelae resulting from the injuries, the long-term effects are unknown.

And the final question being: Do these

data support the safety of the EMBOL-X intra-aortic filter?

Question 2. The primary effectiveness endpoint in this trial was to demonstrate that 75 percent of the devices would capture at least one particle during elective CABG or single-valve procedures. This was demonstrated in the study.

There was no demonstrated reduction in any category of clinical adverse event in this well-controlled 1,289-patient trial. Please address the following concerns:

1) Can this method of embolic entrapment, from this study or elsewhere, be extrapolated to clinical efficacy?

2) Do these data support the effectiveness of the EMBOL-X intra-aortic filter?

Question 3. Do the study data support an appropriate risk/benefit profile?

Question 4. One aspect of the 510(k) review of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse effects.

Please address the following questions regarding product labeling:

1) Do the Indications for Use adequately define the patient population studied? For example, should the patient population receiving this device be limited to the same patient population utilized in the study--for example, nonemergent, patients over age 60, and first-time isolated valve or CABG patients.

2) Are there any other restrictions that should be placed on the patient population receiving this device?

3) Based on the clinical experience, should there be additional Contraindications, Warnings, and Precautions for the use of the EMBOL-X intra-aortic filter?

4) Should the labeling include specific study information such as: no reduction of clinical events were noted in a 1,289-patient clinical study; and the EMBOL-X device appears to increase the rate of endothelial injury?

5) What should the labeling include regarding the use of ultrasound both before--for assessment of the aorta--and after--monitoring of injury--the use of the device?

Question 5. Please provide any other recommendations or comments regarding the labeling of this device.

Question 6. If the data provided are not adequate to support safety and/or effectiveness, what additional data, analyses, or study would you require?

Thank you.

Questions and Answers

DR. TRACY: Does that complete the FDA presentation?

MS. WENTZ: Yes.

DR. TRACY: Does the panel have any questions for the FDA before we move on?

DR. LASKEY: I have one question to the engineer. Maybe it is trivial, maybe not.

Nitinol and its thermal properties--there is a nitinol frame here. Patients are generally cooled when they are put on bypass, hearts are cooled, and so on and so forth. Is there anything happening with the--should we be concerned about any change in function or configuration of the frame here?

MS. WENTZ: That is a very good question, and actually, that was brought up in a few of the

stent studies a few years ago, when you place stents that have nitinol in them because patients are cooled down as well. And I believe from that, I did not review that from a material standpoint--our OST scientists did--but that was looked at, and the temperature that the patients are cooled down to does not affect the nitinol.

DR. TRACY: Dr. Marler?

DR. MARLER: In Dr. Swain's discussion of the myocardial infarction data, I may not have been able to see the complete slide, but I didn't have the impression of the same difference between the groups and the incidence of MI, and I was wondering where that information came from.

DR. SWAIN: I think in your pack, you can talk about total MIs or Q-wave versus non-Q-wave MIs. So that is the difference. I believe the sponsor's presentation was total MIs, and my presentation was to pick out Q-wave MIs and stroke versus the lesser injury.

Do you want that slide back up? I might be able to do that.

DR. MARLER: I might be looking at the wrong table; I am looking on page 35, Table 62.

[Slide.]

DR. MARLER: Okay. It was a problem of not being able to read the slide, because I couldn't read the X axis. So it is clear now. I'm sorry.

DR. TRACY: Dr. Krucoff?

DR. EDMUNDS: Julie, when they did these epi-aortic ecograms, did they look at the area of the cross-clamp with the core laboratory look, where they were able to see things that nobody else could see?

DR. TRACY: Can we ask that during the open committee discussion, please? We haven't quite gotten there yet. I just don't want to mix the FDA with the sponsor.

DR. EDMUNDS: I just asked Dr. Swain. I don't know why--

DR. TRACY: If she doesn't know the answer, then, let's just hold the question.

DR. SWAIN: Yes, it was looked at. And the injuries are not seen by the surgeon--I didn't look at my screens very much when I was busy closing up and getting up pumps. It was identified at the institution, I guess.

DR. TRACY: Dr. Krucoff?

DR. KRUCOFF: I have a question for Dr.

Gray.

Gerry, in your particles analysis--I probably just didn't connect when it started--but to me somehow, the elimination of particles by the filter would ostensibly be associated with a reduction in clinical events; if you got them out with the filter, presumably, you are saving the patient that avalanche effect.

And somehow as I looked at these--is that where the divergence in total number of particles captured--well, I'm confused.

DR. GRAY: Let's go back to Slide 2.

DR. KRUCOFF: Yes, because that's where it started.

[Slide.]

DR. KRUCOFF: So is your expectation--is what you are testing here that if you get more particles out with the filter, you are more likely to have a composite event?

DR. GRAY: We have a problem here with the endpoint, because we all would like to see the clinical endpoint, and what we have is the particulate capture. My line of reasoning here was let's see if somehow we can justify using particulate capture as a surrogate for some

clinical outcome that we are interested in, in this case being the composite adverse events.

So I am trying to see if there is some correlation between whether or not particles were captured in a patient and did that patient have an adverse event or not.

DR. KRUCOFF: Okay, but the assumption here is what I am trying to get at, Gary--

DR. GRAY: I guess the assumption is that if removing particles does anything, we would expect that where the particles were removed, we would be reducing the composite adverse event rate. That is my assumption.

DR. KRUCOFF: Well, I would suggest that the assumption is if particles are a surrogate for bad things happening, that that is what happens in a control population--if you have 1,000 patients with no protection, some of them are going to have very few particles, and they would have fewer events; others are going to have showers of particles or big particles, and those would have clinical events.

The trouble is that as you start removing particles, if you capture very few particles, those may be patients who have very few particles, and if

you capture a lot of particles, those might be patients who would be high risk whom you are protecting.

I just don't see how this would even begin to test that, because the assumption is that somehow particles removed would correlate with badness in the same patient population, and--

DR. GRAY: I agree that--we wish we knew the denominator here, right; we wish we knew for any patient how many particles really there were present, and then we would have some idea of the effectiveness of removing those particles, so we could say that somehow, the amount of particles released in that patient is some indication of their potential risk for an adverse event, and then we could try to figure out, okay, if we remove a certain proportion of them or if this device can remove some proportion of them, what effect would that have on the outcome. That's what I wish we knew. But we don't know that. We don't really know at all--and you are right, we don't know for any patient--if the device captured one particle, that could be the only one that was released, or it could be one out of thousands. There is no way to tell that with the data that we have.

So I admit I was on a bit of a stretch here to try to figure out is there any way to take the data that we do have, which is purely the number of particles captured, and relate that to whether or not there was an adverse event. That's why I went on to the next slide, which was just that.

What is missing here is--you are right--what we really would love to know is the underlying information for each patient as to how many particles were actually released and how much risk was that patient exposed to. But we have nothing to tell us that as far as I know.

DR. KRUCOFF: Okay. Can I ask you--because when I actually walked through these slides, what I ended up sitting here thinking, which I took as different from what you were suggesting, is that although I agree it is a stretch, this might be taking as an imputation that you can take patients who are at much higher risk, i.e., the higher -particle group, and pull them down to a line of identify with patients who are at much lower risk, i.e., patients who have fewer particles, in a population where you are not allowing these particles into the systemic

circulation--you are removing them.
Is that wrong?
DR. GRAY: I can't say whether that is wrong or right, because if I understand correctly, what you are thinking is that somehow this mesh puts a limit on the amount of particles that are released, that actually escape through into the circulation, and therefore, that would be nothing but a good thing.
Is that a correct interpretation of what you said?
DR. KRUCOFF: But that would be one notion, I think, of the whole generation of distal protection devices, that basically, the more you get out with the device represents some sort of surrogate incremental protection afforded the patient.
DR. GRAY: Yes. And that sort of gets back to my first set of ways of judging the results of the trial. And you can infer in your own mind that removing particles is undoubtedly a good thing and that the device only needs to be shown effective as a tool that removes particles, and that's all they care about, therefore, I'm happy with.

On the other hand, we have the internal to the study comparison between the treatment and the control group, where it was remarkably uniform, remarkable similarity in the adverse event rates across the board.

So how do we make that judgment--that's why I started out with that, because I think that is really the whole crux of the--

DR. TRACY: The less kind interpretation, Mitch, would be that it doesn't matter if you remove particles--the risk is the same--

DR. KRUCOFF: Yes.

DR. GRAY: That's right.

DR. KRUCOFF: Understood.

DR. TRACY: Okay. Can I ask Dr. Wentz to clarify--you mentioned that bench study, some design concerns and/or test method concerns remained that may be related to the endothelial injuries. Could you expand on that just a little bit?

MS. WENTZ: First of all, it is not "Doctor" but thank you.

When this submission first came in, we looked at the test methods and the results and procedures and all that, and everything looked

okay, and we let the study go on. It wasn't until we started focusing on these endothelial injuries that we backtracked and said, okay, what could some of the possibilities be for these injuries.

Dr. Sapirstein and myself re-reviewed all of those test methods and found that there were a number of them that could possibly be related to those endothelial injuries. So we just sent those questions to the company in the form of a 510(k) Additional Information Letter--and did that come back already--no--they are still formulating the answers to those.

Does that answer your question?

DR. TRACY: I guess so. I'm not sure what the design questions are--whether it is that the thing is too stiff or is too--is there some fundamental problem with this thing that you are asking them to clarify?

MS. WENTZ: Yes, that's basically it. When we tried to repeat their test methods using the sample device that we had, some of the forces that we felt were not anywhere near some of the forces that were on the paper that they said they had recorded. So we just asked them to clarify some of their test methods and procedures in light of the

endothelial injuries.

DR. TRACY: Thank you.

Are there any other questions?

Dr. Aziz?

DR. AZIZ: Let me ask Julie a question.

Julie, these endothelial disruptions--I'm sure the company will focus on that later--in your review of the data, where were they occurring? Was it at the tip of where the net is? Where is it, and what do you think is causing it?

DR. SWAIN: Right. You know what you can see on a TEE; essentially, you are blocked off because of the airways so that in the area examined of the ascending aorta, they occurred. Some of them occurred proximal, where the clamp was, but I didn't see it, or don't recall it being broken out that much; but they certainly did occur in the area where you have aortic manipulation.

And I think also, in answer to Dr. Krucoff's question, the patients who had the biggest amount of atherosclerosis were screened out--that group wasn't studied. So the kind of catch-22 is that maybe they would benefit more, but again, aortic manipulation in the presence of known atherosclerosis, from all the data and the work of

20 years from Dr. Kouchoukos, is what we all learned we shouldn't do.

DR. AZIZ: And then actually looking at the ECO that was presented earlier, it seems like there were two different types. You had this fibrinous strand sort of waving at you, and then you had like an intramural hematoma on the wall. Maybe we'll look at that later.

DR. SWAIN: Yes. You may ask the sponsor about the intramural. I didn't remember seeing that. It's kind of like in surfing, we use the term "dings"--it is an aortic "ding"--no clinical consequence as evaluated in this short-term study.

Open Committee Discussion

DR. TRACY: At this point, let's move on to the open committee discussion. I think there are lots of questions waiting to be asked.

I would just like to remind everyone that this is a premarket notification or a 510(k) submission that is being brought to the panel at this time. And at the end, the FDA is asking for recommendations and advice. There will not be a final vote. And the two lead reviewers were Dr. Marler and Dr. Edmunds.

Dr. Marler, if you would like to lead off

with questions for the sponsor.

DR. MARLER: Okay. I guess this very technical--I still have this question comparing table 7-18 and 7-19. I tried to read and understand, and I'm sure there is an explanation, but for adverse event under NIH Score greater than 4 in the control group, there are 13 in table 7-18 with 644 patients, and then, when the sample size is reduced to 620, there are more--16. Is that because you are including events that occurred after the first exam?

DR. ALLEN: I think it's a very good observation. There were very little times when the initial NIH score was applied. In the initial design of the study, we had hoped to have a 24-hour evaluation on every patient, but it became quite obvious as the study progressed that that wasn't practical. Patients were [inaudible] and so forth.

So discussions then allowed us to do our first evaluation at 3 plus or minus one day. So that initial evaluation is variable in time.

When you look at the 7-day evaluation which is applied evenly among both groups--call it the end evaluation of the New York Stroke Scale--the rates were essentially identical between

the groups--2.6 was [inaudible].

DR. MARLER: So, then, which one do you think most accurately reflects the strokes that were due to the cardiopulmonary bypass procedure and the surgery? Is it Table 7-18?

DR. ALLEN: That's a very interesting question, because when you look at actual frank stroke after cardiopulmonary bypass, Dr. Kuntz in his presentation outlined the multiplicity of reasons for why patients have strokes. The stroke rate overall in our study was about 2.5 percent. It is interesting that if you look at the time course as to when those strokes occurred, only about half of them actually occurred greater than 24 hours--the patients woke up neurologically intact, and at day 2 or day 3 had an event.

So the device's potential to impact frank stroke is with the operation. When we did an analysis, for example, on the impact of atrial fibrillation, 60 percent of patients who had stroke also had atrial fibrillation, which we know is a potential indicator for stroke.

Dr. MARLER: The neurologist was looking throughout this for any description of the strokes or any further analysis, even breakdown as to

hemorrhagic or ischemic--did I miss it? Is it somewhere in the writeup, or was there data available to me on how the strokes were diagnosed as to their type?

DR. ALLEN: I don't believe we broke the strokes down, and I don't--

DR. MARLER: For severity?

DR. ALLEN: --for severity as far as whether it is a hemorrhagic stroke or--

MS. CHANG: These are all ischemic strokes.

DR. ALLEN: --but they were adjudicated by a blinded events committee and felt to be related to surgery.

MS. CHANG: We provided narratives in the 510(k) filing on these.

DR. MARLER: Okay. But those aren't in the packet here.

MS. CHANG: No.

DR. MARLER: Okay. They are not very interesting reading to the cardiovascular surgeon, I'm sure.

[Laughter.]

DR. MARLER: So, what I am looking for is an argument as to the logic of--I mean, we have

said that there is not a surrogate marker for safety. What is the clinical efficacy--what is the benefit to the patient--I mean, what's the talk on this? What are you expecting--why do this? It seems to me the study has shown that it is as good as doing nothing. But why is it better, and what are you thinking?

I was concerned that the discussion about the cognitive outcomes indicated--which I thought would be an obvious possible benefit--it was stated that that wasn't really thought of as a potential benefit. So I am a little unclear on the thinking of really what this study means to the patient.

DR. ALLEN: We grappled with that, and I thought Dr. Kuntz tried to outline that in his presentation with regard to study design.

You know, intuitively, reducing the particulate emboli load is a good thing, but we grappled in the design of the study with the very question that you are asking: How can we demonstrate an efficacy endpoint?

And the conclusion was that, for example, unlike the SAFER trial where you had a very specific marker--CPK isoenzymes that affected a very specific end organ--with the exception of

perhaps serum creatinine, we didn't have specific sensitive markers that might detect subtle clinical changes in patients' outcome. So we ended up with a design trial that essentially looked at safety equivalency to show that the device wasn't causing harm and that the particulate capture was the efficacy endpoint, and that capture of particles was a good thing.

You know, the difficulty of designing a trial comes down to what can be practically applied and logistically applied across multiple centers, and the one power calculation that Dr. Kuntz did--if you look at just, for example, frank stroke and assume you have a 3 percent incidence of frank stroke, not all of those strokes occurred in the operating room, so you wouldn't even expect that the device would prevent all of those strokes, but let's assume for argument that the event rate was 3 percent. A 20 percent reduction in that 3 percent rate would require a sample size of a little over 22,000 patients to demonstrate that.

So you weigh what seems clinically intuitive with the practical aspects of designing a trial that demonstrates that clinical efficacy. And I think the additional analysis that we

provided--and I make full disclaimer--I take my mea culpa in that I don't make claims of superiority when we look at that additional analysis, but it does provide some element of risk-benefit as to what population this may truly benefit, and it is the higher-risk group that we know as surgeons have an increased risk for morbidity and mortality postoperatively that, intuitively, reducing that embolic load in those patients seems very reasonable, and that additional analysis, when you looked at an endpoint that has a specific marker, i.e., serum creatinine, you began to see clinical ticks that, yes, there is something maybe going on there.

But I agree with the FDA, and I don't want to make claims of superiority. We simply rely on the clinician's intuitiveness that a reduction of this embolic load is a good thing.

DR. MARLER: What can you say that would reassure me or the committee--I mean, we have knowledge that there are instances where something that is really intuitively obvious--blood pressure, arrhythmias, I hesitate to mention, but ECIC bypass I am pretty confident of, in which there is a real obvious case in which the intervention did what it

was supposed to do but it wasn't clear at all, and some people still think it may have actually been harmful but hiding underneath the obvious clinical benefit.

Is there something different about this that would--is there any reassurance you can offer?

DR. ALLEN: No, and I think the panel members are grappling with the same things that I grapple with when I think about this data.

You are absolutely right. There are many instances where your intuition tells you something is good, and a well-designed trial tells you that now your intuition wasn't as good as you thought it was.

In this particular trial, it was designed as a safety study to demonstrate that the device, compared to current cannulation techniques that we use every day in open heart operations, isn't worse, and that particulate capture was the clinical efficacy endpoint.

DR. MARLER: Thank you.

DR. TRACY: Dr. Edmunds?

DR. EDMUNDS: Keith, are you going to be the one who responds, or someone else? On this injury, if we discount the three, one of which was

the scalpel and the other one, a surgeon took a stitch or two, and just concentrate on the 42, most of which were not surgeon-noticed at the time, or anesthesiologist reading the ecocardiogram, whoever it was, how many of those were more than just the endothelium? How many actually got into the media?

DR. ALLEN: I think Dr. Kouchoukos is experienced in this field, so I'll let him answer that question.

DR. KOUCHOUKOS: These were all basically endothelial disruptions. In other words, they are just small fragments of intima.

DR. EDMUNDS: And do you think they were scratches from the nitinol wire?

DR. KOUCHOUKOS: Well, the question was raised earlier about in the filter group, where these intimal disruptions were located, and they were distributed throughout the ascending aorta. Some of them were clearly related to the filter, but others occurred in the mid-aorta or perhaps in the more proximal part. So they would be expected to have resulted from other manipulations of the aorta, and that's basically why they occurred in the control group.

DR. EDMUNDS: And that's why they occurred

in the control group, too.
DR. KOUCHOUKOS: That's what I said; that's why they were present in the--they were present in 2 percent of the control group. And I think--
DR. EDMUNDS: right. So how long do you think it took for that to heal?
DR. KOUCHOUKOS: Well, we don't have followup ecocardiograms or epi-aortic images to know the answer to that. It is also important to note that only one of these was detected by transesophageal ecocardiography. They were all detected for the most part by epi-aortic scanning. So you wouldn't see one of these with a transesophageal, and certainly not with a two-dimensional surface ECO.
DR. EDMUNDS: Isn't it a stretch to call this an "injury"?
DR. KOUCHOUKOS: Well, it's a good question. We termed it a "disruption," but I think others would term it an "injury."
DR. EDMUNDS: Gosh, I would consider it an overinterpretation of the ecocardiogram myself, if it were one of my cases.
Does anyone really think that this will

progress to any problem downstream for the patient?
DR. KOUCHOUKOS: I think, again, it is important to put it in historical context. These endothelial disruptions have been occurring since we started doing cardiac surgery.
DR. EDMUNDS: Exactly.
DR. KOUCHOUKOS: They have been there forever. And from what we know about the outcomes of patients who have cardiac surgery, they are probably of no significance. We know that an intra-aortic dissection is a catastrophic event, and we know how frequently that occurs, and it is very rare. And I think to extrapolate to what happens to the endothelial disruptions is hard, because they are not as significant as the others, and we really have no way of following what happens to them. We would surmise that they probably heal eventually, but we have no hard data to support that.
DR. EDMUNDS: In your experience as a very busy cardiac surgeon over the long period, which is the greater injury--the cross-clamp injury to the endothelium, or produced by this filter--in your opinion? I know you don't have data, but you have a lot of clinical experience.

DR. KOUCHOUKOS: Well, I think that what, if anything, we have learned from this study, and as we have learned from our own clinical experience, is that we want to manipulate the ascending aorta as little as possible. And certainly a cross-clamp is a major insult, if you will, to the ascending aorta. It is exposed to a lot of surface of the aorta, with the potential for dislodgment of atheromatous debris, and a side-butting clamp is the same.

DR. EDMUNDS: So you think the clamps are a bigger injury?

DR. KOUCHOUKOS: I do.

DR. EDMUNDS: Now, as I understand it, the company does not intend to make any statement on the labeling about--am I out of order already--

DR. TRACY: No--not yet.

[Laughter.]

DR. EDMUNDS: --okay--about clinical benefit; is that correct?

MS. CHANG: To both of them, yes.

DR. EDMUNDS: Okay. There is no evidence that particulate emboli to the brain is good, so it is logical to assume that reducing it is at least not bad and is probably good.

What percentage of the atherosclerotic emboli to the brain would you guess this filter when it is deployed decreases from some unknown hole? What would be your clinical estimate? I have one in my head.

DR. KOUCHOUKOS: I'm not sure I understand your question, Dr. Edmunds.

DR. EDMUNDS: What percentage of all the emboli that go to the head from surgical manipulation doing a case do you think this filter catches?

DR. KOUCHOUKOS: Well, it catches a different amount of material from each patient, and I think you saw that. There are patients who release small numbers and small sizes of particulate matter and others who release large amounts.

From what we know from Dr. Barbut's studies and from our own experience, I think about 20 percent of those have the potential to go to the cerebral circulation, and a percentage of those would probably be dispersed to the brachial arteries and not enter the brain, but in her study, I think on overage, about 9 percent of the emboli in one small study that were released went to the

brain.

DR. EDMUNDS: Well, I would answer the question a little bit differently. Fourteen percent of the cardiac output goes to the brain. That is physiology. So we would presume that the amount of emboli would be the same, unless there is some streaming.

We also know that the injury to the brain is due to a whole lot more than atherosclerotic emboli--complement activation, cytokines, regional profusion differences, temperature movement, and all that sort of thing go into cumulative brain injury--but from what I know, I think you are only catching a fraction of the total exposure of the brain to atherosclerotic emboli. I have no idea what the fraction is exactly, but I suspect it is less than 50 percent. Would you disagree strongly with that, any of you?

DR. KOUCHOUKOS: No.

MS. CHANG: No.

DR. EDMUNDS: My case rests.

DR. TRACY: Thank you.

We'll go around the table with panel members to allow them to ask any questions they have for the sponsor, and we'll begin with Dr.

Pina.

DR. PINA: I have a question about the renal dysfunction. I see your definition of renal insufficiency being an increase of greater than 2 or 50 percent increase, and I may have missed it here, but do you actually have the values of the creatinines? Do you have the mean values--because so many things happen around surgery with drugs that we give that can alter renal function back and forth, and yet to those of us who take care of these patients afterward, that is a very significant point, the rental function.

DR. ALLEN: I think the important aspect of that is that it is 50 percent above baseline. I think one of the things that the investigators wanted to put into this study is that if you start out at a creatinine of 1.8 and go to 2.0, it's not fair to count that as a patient who has renal insufficiency, but it is a 50 percent increase from baseline or any increase above 2 that is important.

DR. PINA: But I can also do that if I give a lot of diuretics to a patient in a perioperative period.

I would like to know what happens to those patients later. Do you have any followup after

those 7 days about the renal function?

DR. ALLEN: Actually, what you see is that renal function, as you well know, worsens after cardiac surgery. There were some patients who required dialysis, but renal function returns to normal.

The beauty of this is that this was in a randomized trial, so the same variables like did you start Altase postoperatively, at a time when you are diuresing a patient. You make the assumption--and it is the reason you do the randomized trial, to allow for those variables to be adjudicated.

DR. PINA: My point about followup with the renal function is it may help to differentiate the things that are strictly just the drugs that we do, or is it really emboli events to the kidneys, which may not result.

DR. ALLEN: I guess I don't know that our data can help you answer that. All I know is that in a randomized trial, when you look at the safety endpoint, one of the endpoints in the composite was renal insufficiency, and you can't make a statement that renal insufficiency was significantly reduced. Only when you look at the higher-risk patients do

you begin to see trends or ticks in favor of a reduction of renal insufficiency. But you have to assume that if you did everything identical in the two groups except one got a filter and one didn't, and you see the impact that renal insufficiency has on length of stay--and you know that from your clinical experience--in our situation, if you had renal insufficiency in our study, your length of stay was almost 15 days compared to 7 if you didn't have renal insufficiency. So it does have a dramatic impact.

DR. PINA: I have no further questions.

DR. TRACY: Dr. Ferguson?

DR. FERGUSON: First, I want to congratulate the presenters, both your group and the FDA, for very lucid presentations.

I have a couple of questions that relate to the particulate matter. The difficult is, as has been mentioned many times before, that we don't know what the denominator is, whether in the total spectrum of open heart surgery on a person who has atherosclerosis or some clot in the ventricle, whether a total screen would capture 1,000 particles, 500,000, whatever. So that is of a little concern, and I will get back to it in a

second, relative to the time that you deploy.

But first I want to ask about in the Higgins above-5 group, did you note that there were more numbers of particles in that than you would expect? I missed that; I'm sorry.

DR. ALLEN: I think that's a very good question. to be honest, I'm not sure we did that analysis. We looked at the Cleveland Clinic score that was prespecified in those papers, picked their number of 5 and used that number.

DR. FERGUSON: You would expect that would be the case. And that gets to my second question, which is that the instrument was not stressed to the max, if you will, because it was not purposely p ut in the kinds of aortas that everybody is seeing today. I think that's a fair statement--or is it?

DR. ALLEN: Yes, sir, and part of the exclusion--although we didn't specifically exclude patients with, for example, Grade 4 aortas--the exclusion criterion is that if you did your stronotomy and opened the patient, and it was an aorta that the surgeon did not feel that he could clamp or wanted to clamp, then, patients were excluded.

So you are absolutely right, it did not necessarily even apply to the worst patients.

DR. FERGUSON: The issue, then, for us is that--I don't know how we would approach this, and FDA will tell us--but this obviously is going to be used in the very severe aortas all the way up to the porcelain aorta.

Nick, do you want to respond?

DR. KOUCHOUKOS: Well, there is certainly the potential to use it in those patients. I think it would depend on the comfort level of the individual surgeon. But I see no reason why it would not be used in severely atherosclerotic aortas. We didn't encounter many patients who fell into that category by virtue of the patient group that we were elected to study.

DR. FERGUSON: It gets to the disruption issue and whether there are going to be more disruptions in that group. I suspect there will be, because you say they--that gets to my next question, if I could go on to that, and that is you have had more experience with epi-aortic ECO than anybody in the world, I suspect. Have you seen these disruptions in the series that you did prior to this study?

DR. KOUCHOUKOS: One of the interesting things about epi-aortic scanning is that we have been using it for a long time, but we never for the most part until we began this study or until we became aware of some other publications did another scan after the completion of the procedure. You see, that's the difference with this study and how we have come to identify these endothelial disruptions.

The point I made earlier is that it is quite likely that if we did epi-aortic scans on patients after the procedure, we would have found these endothelial disruptions a long time ago.

DR. FERGUSON: So my next extension of that would be in your opinion, the group's opinion, should epi-aortic scanning before and after use of this device be recommended in the use of the device.

I know that a lot of people don't use epi-aortic scanning, and I understand the ramifications there, but from a safety standpoint, I am just bringing that up.

DR. KOUCHOUKOS: Currently, epi-aortic scanning is not standard of care, and it is my impression that it probably won't be for the

foreseeable future. And based on what we know about the outcomes of the patients who develop endothelial disruptions, I would say it would not be necessary.

DR. ALLEN: I think as a side that Dr. Ferguson did not use epi-aortic scanning--we do 1,800 pumps a year at our hospital, and epi-aortic scanning certainly is not standard of care by any means. My personal belief and how I would use this device, epi-aortic scanning is not additive.

The thing that I would--

DR. FERGUSON: If the disruptions are only seen with epi-aortic scanning, and if most people in the study didn't use it, you don't know what the real incidence of that is. That's what I'm getting to.

DR. ALLEN: I think, though, that the corollary to that is that we did see endothelial disruptions, and--

DR. FERGUSON: You did with--

DR. ALLEN: --with epi-aortic scanning--and you are right, those did occur--but I think you have to put that in the clinical context of what those mean, and the two endothelial disruptions that were repaired at the single center

very early on in the series were--as Dr. Kouchoukos said, there was really no historical background as to what those meant, and they acted upon their--I won't say clinical inexperience--but their lack of historical background about them.

The 10 endothelial disruptions that were subsequently identified by surgeons, none of those surgeons acted on those, because they had been educated and kind of knew now what they were seeing, and they didn't overreact to--I won't use Dr. Edmunds' term--but as an overinterpretation of a very sophisticated imaging technique.

DR. FERGUSON: I understand the data very well. The next question is what percent of the sites used epiaortic scanning before and after, because that to me would be the gold standard to really define whether this is going to turn out to be significant.

DR. KOUCHOUKOS: Someone can provide me with the exact number of patients who had scanning in this study, but I think it is over--is it 500 or thereabouts--

MS. CHANG: It's over 500.

DR. KOUCHOUKOS: So about 500 of the patients had epiaortic scanning. And again, I

think it is important to emphasize that 78 percent of these endothelial disruptions were not seen either by the operating surgeon or by the anesthesiologist, who is taking perhaps a little closer look at these ecocardiograms intraoperatively. They were not recognized. They were only recognized by the core laboratory.

DR. FERGUSON: I see. Thank you.

That's all I have.

DR. KOUCHOUKOS: Four hundred and nineteen patients had epiaortic scanning.

DR. TRACY: It's exactly 12 o'clock now, so at this point, let's take an intermission for lunch and resume at 1 o'clock.

[Whereupon, at 12 o'clock p.m., the proceedings were recessed, to reconvene at 1:06 p.m. this same day.]

AFTERNOON SESSION

[1:06 p.m.]

DR. TRACY: If everybody is ready, I'd like to resume the open committee discussion.

Dr. Ferguson, were you finished with your questions?

DR. FERGUSON: Yes, thank you.

DR. TRACY: Okay. I'll pass it on, then, to Dr. DeMets.

Open Committee Discussion - Continued

DR. DeMETS: Thank you.

Some of the questions I had have either been addressed earlier or addressed in the questions, but I still have a coupe more.

Could you tell me a bit more about the rationale for the particular delta, the 5 percent that was decided? Obviously, that's very critical in the size of the study you came up with and the goal that you were after. So could you comment on how that rationale went?

DR. ALLEN: Dr. DeMets, I apologize, but if I could have Dr. Kuntz answer your questions, I would appreciate it.

Thanks.

MS. CHANG: Dr. Kuntz can provide more

detail, but that delta was decided on after several meetings with the FDA, and it was mutually agreed upon.

DR. DeMETS: Okay. So this was not something that was based on clinical considerations or what would be important to rule out as a safety issue, or--

MS. CHANG: Not being a statistician, I--

DR. DeMETS: Well, it's not a statistical question. It's actually what clinical difference do you want to rule out, and I'm just trying to understand how the 5 percent was arrived at. There are a lot of statistical implications about that, but how you got to that decision is what I'm trying to understand.

MS. CHANG: The delta of 5 percent.

DR. DeMETS: Why 5 percent.

DR. KUNTZ: The deltas are always inexactly determined in general, and I think that in our decision, with the baseline rate of 15 percent as established, 5 percent is already 33 percent delta, which is kind of on the high end of deltas to begin with, but has been in the range for devices in the cardiovascular arena. But I think that overall, the final arbitrator was that the

clinicians felt that if they could remove emboli and have a plus or minus 5 percent overall event rate, they would accept that the device would remove the emboli, and that was the thing that we passed around, and that seemed to be the logical background to the 5 percent decision.

DR. DeMETS: Okay. I asked you about the [inaudible] issue earlier; perhaps I jumped the gun. I am trying to understand as a non-surgeon what percent of patients who have this surgery in fact release particles. Is it 100 percent of them, or is it half of them?

DR. KOUCHOUKOS: We don't know the answer to that question because we have had until now no way to assess that. Dr. Barbet, who is here, has done some studies with ecocardiography and transcranial doppler suggesting that there is a large number of particles. The issue there is that some of these particles are gaseous and some of them are particulate, so it is difficult to tell.

DR. DeMETS: Well, my question actually has two parts. One, when it is released, how much is there in a patient, but how many patients is it--is it almost always? Is it rarely? I don't know as a non-surgeon.

DR. KOUCHOUKOS: Well, this study would suggest that almost all the patients release--or, at least over the age of 60--release some particulate matter, and it is a spectrum, obviously, depending to a great extent on the severity of atheromatous disease in the ascending aorta would determinate how many particles and their size are released.

DR. DeMETS: The second part of the question which is important is given that they are released, what percent does this device capture. And at least in the FDA review, there was a suggestion that if you average 5 to 5.6, whatever it was, and it was 25 to 30 particles, that suggests a 20 percent or so capture rate. Is it higher or lower than that, because if there is a lot of it, and you aren't getting much of it, then, what are you really accomplishing, I guess is what I am trying to understand.

DR. KOUCHOUKOS: Well, again, it is hard to say. This filter is occlusive, so theoretically, at least, it should capture all of the particles that are released proximal to where the filter is located. So we would think that the capture rate should be high.

DR. DeMETS: Okay, thank you.

Another question is that this trial obviously is not blinded, and when you are trying to establish equivalence, or at least safety equivalency, one of the challenges is always that you have to do a high-quality study. If you don't do a high-quality study, then it is easy to show or easier to show two things being equivalent, whatever you define as equivalent.

So my question is given that this is clearly an ongoing study, what comments can you make about that there wasn't some bias between the two procedures, if you will. I'm not sure it is possible to introduce bias, but at least the potential seems to me to be to do that. So can you help me on that a little bit?

DR. KUNTZ: Yes, sir. It's an excellent question.

In any study where we are using a device, especially a surgical study, it is impossible to blind because the ethics would make it a sham and impossible.

So most of the time--and this goes to the question about our endpoint per se--the endpoint had always been focused on safety. And we talked

earlier about the fact that we had included the myocardial infarction part because that is a safety endpoint that you would be interested in--not necessarily an efficacy endpoint, because the filter is north of the heart there.

But the bottom line is that the components of the endpoints were all hard endpoints, that is, they could be determined by an external adjudication committee that would hardly be malleable by someone who had a conflict of interest. That is, myocardial infarction is a new enzyme elevation or change in the EKG, death is death, stroke is stroke. These are very hard, nonsubjective endpoints, and they tend to help minimize the influence of bias of unblindedness.

So we tried to make sure that the constellation of [inaudible] endpoints were in fact hard endpoints, none of which would be too subjective or that would lend itself to too much bias.

DR. KOUCHOUKOS: Can I amplify on that for just a moment?

DR. DeMETS: Sure.

DR. KOUCHOUKOS: The examiners for the neurologic events were blinded as were the

patients. So at least the neurological assessment as blinded.

DR. DeMETS: Well, I think that to your credit, you worked very hard on that end of the process. Again, I ask the question as a non-surgeon, but one can imagine that if you had a bias about a device, you could be more careful or more careless, if you will, in actually doing the surgery and therefore artificially introducing one group looking better than the other. And like I said, maybe that's an ignorant question for a non-surgeon, but the issue is how you deliver it also affects--even if you have everything blinded, and the ascertainment bias is minimized--how you deliver the therapies can also introduce bias, and I'm just trying to understand that process.

DR. ALLEN: Let me give you a real example where what you are saying could be totally true. Let's say, for example, as a surgeon, I randomize my patient to not a filter. I could change my technique, for example, of the operation and do less proximal anastomosis or, for example, not use a side-biting clamp, or do things that might do what you are saying; but you will recall that in the demographics, we really specifically looked at

those things, so that the things that the operator could vary that might impact the outcome, such as doing T-graphs off the mammary instead of putting them on the aorta, were not occurring, or not using a side-biting clamp, were not occurring.

It is a very valid question, and I think the size and scope of the study, we did the very best job we could, not only from a design standpoint but then from an analysis standpoint of the operative data, to ensure that that wasn't going on.

DR. DeMETS: Okay. I think that answers most of the questions I had--and I still struggle with the issue of the clinical relevancy in the surrogate, but I'm not sure what you can say that you haven't already said.

Thanks.

DR. TRACY: Dr. Aziz?

DR. AZIZ: I just have a few questions, some sort of technically related.

When I look at the cannula, you have the side arm, and when you cannulate, do you get air in that side arm, and how do you de-air that?

DR. ALLEN: The concern about air comes from two things, primarily in that the filter is

set in a heparin solution and then retracted up into the device. That still doesn't ensure that there couldn't be air within this cannula--

DR. AZIZ: But when you initially cannulate, when you put that cannula in right away, the first time around--

DR. ALLEN: You de-air by taking--there is an opterator that goes in the sideport, and it is de-aired through that, through that one-way valve, so when you pull that out, the opterator allows the air to flush out, and then, the cannula itself is de-aired as I described earlier, with venting through this air release plug.

The opterator also has the little--I call it an air release plug--it is the little wet plug that allows the air to go through it, so it actually vents through that plug when you put it in.

DR. AZIZ: And that filter comes up at the time that you have taken the aorta cross-clamp off, so whatever is there in the ascending aorta, you capture.

DR. ALLEN: Right. The filter is inserted and deployed right before you take the cross-clamp off.

DR. AZIZ: So at the time that the protamine is being given, this filter is down, or is the filter mesh still up?

DR. ALLEN: No. The filter has been withdrawn, and most of the time, patients have been decannulated. In my center, we decannulate before we give protamine. But if you leave your cannula in when you are giving protamine, the filter has been withdrawn.

DR. AZIZ: It has been withdrawn. All right.

Let me just ask a few more questions, then. When you were giving your talk, you showed, obviously, two extremes--one with the flap of the aortic dissection, which I think anybody could see. The other side-by-side sort of TE, the surface ECO that you had, there were two--one that had these strands sort of waving at you--it could be fibrin--but the other one--and maybe we could have one of the ECO guys look at that with us--it seemed to me like there wasn't a disruption in the intima, but that there was a gap or a gray zone in the actual media itself.

Could we look at that?

DR. ALLEN: Dr. Weissman, who was

our--while we are teeing that up, if you would like us to show that, we can have Dr. Weissman go over that specifically, and Dr. Kouchoukos might comment on that since he does an extensive amount of epiaortic imaging.

DR. KOUCHOUKOS: All of these ECOs were reviewed by Dr. Weissman, and he indicated to me and I think will indicate to you if there is any question about it that there are no medial injuries at all that were identified. These were all endothelial or intimal injury.

DR. WEISSMAN: That is correct.

I am Neil Weissman, and I was the director of the ECO core lab for this study. I am a cardiologist at Washington Hospital Center.

I have no financial conflict of interest; they gave a grant to the hospital for my work on this.

There have been a number of different points brought up, and I think they have been answered very well, methodological issues and the extent of these endothelial disruptions and what they look like. So as we boot this up, let me just go through a couple of those things.

DR. AZIZ: Sure.

DR. WEISSMAN: People are asking about the methodology, and the methodology--and I wrote the protocol--was to do the scanning in a transverse manner, starting right proximally and capturing proximally at least 5 beats, and then moving one centimeter at a time, capturing 5 beats one centimeter, and so forth. So it was pretty methodological. And then, you do transverse imaging across the ascending aorta.

As that was done, it had to be annotated on the screen or verbally to let me know where they are, and that's how we got location information.

What you saw--were you referring to this picture or earlier on--

[Slide.]

DR. AZIZ: There was another one.

DR. WEISSMAN: Yes. I think one of the things--I don't know if it came through completely--was that this is the more typical thing, which I have to admit I have trouble seeing here. There is a little wiggly right over there--and you have got to turn the lights down.

These images in the core lab were reviewed three times--once by a technician, who would write down their preliminary results; then, independently

by me; then, after I reviewed it, I looked at what the technician said to see if I missed anything and went to the spot where the technician thought they might have seen something to see if I missed anything.

That is why I think 78 percent of these things were not seen by the anesthesiologists or the surgeons at the time.

So I think the terms used here--"strands" and "dings" and "footprints"--are all pretty accurate.

[Slide.]

DR. WEISSMAN: So this is worst case scenario here. Where you see that thing sort of flipping is definitely among the worst case scenario. These, you could see from across the room on a projection with the lights on, okay? This was not the typical thing.

So, show me what area you are concerned about?

[Dr. Aziz indicating.]

DR. WEISSMAN: Actually, you can tell that that is coming away from the wall. Right there, you see it is coming away from the wall. That is not even part of the wall. The intima is that very

light ECO within it. The intima there is probably on the order of 2 or 3 millimeters thick, and it is the ECO-density of the flap that is being lifted up.

That is essentially a monolayer, because the intima is so thin that you aren't seeing it. That is extra-aortic that you are seeing that little lifting.

DR. AZIZ: Okay, good. Again, now that in a sense we have identified that you do have these endothelial disruptions, in my own mind, apart from the sites where you have an aortic cross-clamp on them, it could happen either in the control group or in the other group, but in the group where the filter is in place, how do you think that is causing that? Do you think it is the tip of the sheath that you are putting in, and is it occurring at the posterior wall of the aorta?

For me, that is an important issue.

DR. WEISSMAN: And I'm going to defer--since I was not in the operating room, I'm going to defer that to the surgeons to comment on. Again, the results show that there were these little disruptions distributed along the whole ascending aorta. To conjecture how they arose, I'm

not going to do that; I just read the images.
DR. KOUCHOUKOS: One has to assume that some of these were caused by the filter itself, although clearly not all of them were, even in the filter groups, because we saw them distributed in areas where the filter was not located.
The metal rim of the filter, it is conceivable, could create a small intimal disruption, and that is probably the explanation for why they occurred.
DR. AZIZ: But clearly, the goal of the filter is to prevent the emboli going upstream when you take the cross-clamp off. But I think as was mentioned in the FDA presentation, you could envision where particulate matter is caught in that mesh. You take the aortic cross-clamp off, and blood from upstream obviously hits the mesh on the other side and dislodges particles going downward, and maybe that is what is responsible for the Q-wave MI.
What do you think about that?
DR. KOUCHOUKOS: It is theoretically possible, and I think that is one--it is fortuitous that we didn't look at myocardial infarction, but again, we found no difference in the prevalence of

myocardial infarction--

DR. AZIZ: But theoretically, it doesn't protect against that, and it could predispose to something going in the reverse direction.

DR. ALLEN: Actually, I spoke with Dr. Ferguson, and the design of the filter is a windsock design. Myocardial infarction was specifically put in as a safety endpoint for concerns for that very point. But in designing that windsock which drapes down over--it is like my son does when fishing for tadpoles--you are catching them in the windsock that falls down below, and you wouldn't expect when you have that pressure change for that to blow it out of that windsock as you would, for example, if it were a flat filter, like a seine. And that's why it was designed like that.

DR. AZIZ: Okay. I have just a couple of other questions.

Clearly, the majority of patients--we all do bypass cases,and again, the case mix here was mainly patients who came for bypass surgery--patients who come in for valve operations, particularly aortic valve operations, obviously, you had more calcium and bits of material that

could come off there. When you analyzed your particulate trapping, did you find that it was higher in patients having valve operations, aortic valve versus mitral versus--did you look at that subset?

DR. ALLEN: We did, and what we primarily found was that the vast majority of the histologic material that we have treated was atheromatous.

There is a wide range of material such as calcific material, organized clot that looked like it came from LV or left atrial appendage. We didn't specifically see a correlation between if you had a valve and you had more, for example, calcium versus atheromatous.

DR. AZIZ: Particularly in aortic valve.

The other thing--and I know you can't do it now--but in the study design, the reason you decided not to use TCD monitoring was because--

DR. KUNTZ: I am not an expert in TCD monitoring, but we have discussed this with other trials. It is not clear even in carotid interventions that TCD monitoring can be very helpful, because the high-intensity transience that occurs with that occurs, for example, in every operation for carotid enterectomy, so it is clearly

possibly an overly sensitive measure of high-intensity transience, whatever that is, with respect to ultrasound as a measure of emboli.

Clearly, they do measure emboli, but they may be measuring other things as well, because it is so frequent. Now, there is a lot of interest in looking at transcranial dopplers, and you have to do bilateral transcranial dopplers during that, and I think that might have also been logistically a little bit difficult during the operation. But I think because of the lack of a good sensitivity specificity profile for that test per se, it wasn't used.

DR. AZIZ: Looking at it, you could have seen, for example, compared with the control group--just take the CABs, where you are operating up the aorta--you might have seen less numbers. Clearly, it has been shown that there is a correlation between the number of hits you get on TCD and cognitive dysfunction.

DR. ALLEN: I think the difference is it is hard to know--we can actually see that certainly the filter doesn't capture air or gaseous emboli; it captures particulate matter. And I think that's the hard thing with transcutaneous dopplers, that

it lumps everything as to specks on a spectrum, and whether it is a particulate material or a gaseous emboli, they all look the same.

DR. AZIZ: One other thing--did you see any correlation in people who did get these endothelial let's say injuries--was there a correlation between the thinness of the aortic wall and the size of the aorta--in other words, big, dilated aortas were more prone to getting it?

DR. ALLEN: That's a great question, and actually, what we looked at was whether the size of the filter, which obviously corresponds to the size of the aorta, correlated to an increase or decrease in endothelial disruptions, and it didn't. It just wasn't correlated. So was a larger filter size more prone to causing endothelial disruptions--no. Was a smaller filter size less prone--no.

DR. AZIZ: Thank you.

DR. TRACY: Dr. Krucoff?

DR. KRUCOFF: Let me just ask a couple of quick questions. First, you mentioned at the very beginning of your presentation, I believe, a number for the percentage of patients who were screened relative to those actually enrolled.

DR. ALLEN: Yes. About 15 percent of

patients who were screened were eventually enrolled in the study.

DR. KRUCOFF: Do you have any sense of who the other 85 percent were or why they were--were they eligible but just didn't want to be in a research protocol, or are we really talking about a patient population that comes from 15 percent of the open heart surgery universe?

DR. ALLEN: I think there are a lot of reasons, and you touched on both of them. I think Dr. Kouchoukos' slide showing the types of patients that cardiac surgeons are operating on any more, the cardiologists just don't send us patients who are low-risk, and this was a safety study looking specifically at low-risk patients, and although we enrolled a lot of patients, it took us 20 months to do that. Even in the low-risk group, there certainly would be some patients who opted not to do it, but quite honestly, the enrollment--as surgeons became familiar with this device and saw what they were capturing, enrollment in the study was pretty accelerated, and surgeons wanted to participate in the study.

DR. KRUCOFF: I also just wanted to ask--and thank you for passing the model around,

because that helped me compared to the pictures--as I look at the actual retraction process--and I want to ask you a little bit about the windsock design--when that pulls back in, it seems to me that there is a point when it is partially retracted where not the tip of the windsock but the upper part is actually just kind of flattened. And I would worry about whether that was capable of dumping debris that was not down in the windsock but that was higher up. Have you all--and I just wasn't aware, at least in our panel pack, of any sort or bench-testing or preclinical modeling that has been done to see at what point or what size particles would be dumped rather than captured.

DR. ALLEN: It is a preclinical test, and I'll let Jean speak to that.

MS. CHANG: Yes. We did extensive preclinical tests, and our [inaudible] with the panel package includes the clinical information there. Our preclinical test was with little polyester beads, polystyrene beads. They are like little pinballs, so that when you do this, when you capture, you measure percent capture. And our capture rate was well above 80 percent.

DR. KRUCOFF: Eighty percent. Are these

sticky beads?
MS. CHANG: No. So it is worst case.
DR. KRUCOFF: Because one thing that I take--and this is from looking at your own pictures--is that a lot of the particles that you photographed are not down in the windsock; they are up in the sort of billowing part of the material. When I look at these pictures, and just thinking about what sticky particles, lipid particles or thrombus particles--there is no question that when you get the big one in here, that's down at the tip of the windsock, but a lot of these others are not.
DR. KOUCHOUKOS: When these were removed, the technician who was in the operating room was responsible to collect it, to flatten it out, and to display it; and I suspect that part of that is a flattening effect that was done so that we could get a photograph of the material in the filter. So it is partially related to that.
To the question about possible loss of material, the filter is removed after 20 or 30 minutes, so we would surmise that most of the embolization would have occurred, so it's possible that we missed some of the material that might have passed through the filter as you are removing it,

but I think the probability of that resulting in the loss of a large number of particles would be very, very strong.

DR. KRUCOFF: Okay, I take your point, Dr. Kouchoukos. I was just sitting here looking at this and was thinking about, for example, some of the pressure shifts that Dr. Swain described, and if that was actually not trapped down in the tail but was sitting up in the higher, whether a sudden shift of pressure would dislodge it and do something else.

I think most of my comments have been mentioned. I think the real issue here is a denominator one. In a very complex array of end organ problems, and even the precedents that Dr. Kuntz mentioned in the SAFER study, where the PercuSurge device was used, actually, there was no actual or even attempt to measure particulate capture in that study; that was driven entirely by a clinical measure of an end organ whose effect could be imputed to probably particle capture, but actually, it was purely a clinical measure--and the IIb/IIIa is the same thing. We all sort of suspect in the angioplasty environment that we may create particulate matter that is responsible for end

organ wounds to the heart, but the fact that a IIb/IIIa inhibitor corrects the wounds to the heart to some degree, or that a distal protection system in a vein graft protects the wounds to the heart, we have never really directly measured the role of particles. And what you all deal with in the brain and renal failure and all of the end organ effects, again, I think has been clearly recognized as multifactorial. Some of that is probably particulate embolization, and some of it is probably noncirculatory arrest and predisposing factors and transient hypertension and everything else in the world that comes with that.

So I think that even if we start with the end organ denominator where, obviously, from a patient misery point of view, you would love to find a better way of bringing patients through open heart, the particulate component may only be a subset of that.

And then, my difficulty with the other denominator is that, based on your data, it sounds to me like at least 96.8 percent of patients who undergo open heart surgery have something capturable in a filter, and certainly, 96.8 percent don't have measurable end organ effects. And

again, there is no question when you look at a thrombus as huge as the one you have pictured in one of these pictures, you've got to believe intuitively that you have benefitted the patient by pulling that out of his body rather than letting it go wherever the heck it was going to go.

Ultimately, sorting this out is tough, and I think that point has been made.

And then, the safety issues become more preeminent, because understand what is efficacy is hard.

One suggestion that I would like to amplify as my last comment is if you could in fact correlate--and this is just speaking from my own seat--but if you could correlate that descriptors that you would think, prospectively, for a patient preoperatively, would identify a higher likelihood of having an embolic untoward event, whether they are morphologic descriptors of the aorta or low EFs or whatever you would think would be the ones that would say this population is likely to have more particles, or more frequency of particles, or whatever, and correlate that in your own dataset to a higher capture rate of particles with the filter, to me, that would be at least a first step toward

saying maybe what this filter is able to do is to take higher-risk patients--and again, this is my question to the FDA statistician--one of the things that I think is at least a possible interpretation of what Gerry actually did was to say that what you're doing is taking the highest-risk patients and creating a more linear risk by capturing more particles. It's just that we don't have the descriptors match or really know what the descriptors model would be to say are those really the higher-risk patients or is that just sort of an [inaudible] finding.

I think if you could build that model somewhat, that higher risk of whatever you think would predict embolic events and a higher capture of particles is a correlation, then you could start to think about what would you look for in a smaller venue as a way of really showing a benefit to putting a filter in.

I just want to acknowledge that what is very clear, particularly from our two surgeons presenting, is a clear desire to try to prevent these types of untoward events with an intuitively obvious kind of mechanical approach, but in the face of a real difficult trial planning environment

to the point where I'm not sure that this one study achieves everything that you would want out of it.

DR. KUNTZ: Mitch, can I make a few points about your comments? I think I would actually like to amplify some of your points.

If we look at the SAFER trial per se, there were actually two studies that demonstrated a relationship between the emboli and the outcome. There is the initial John Webb study done, where he actually counted the number of particles, and that was associated with the amount of CK-MB that was elevated. That was the pilot study before the SAFER study.

The second one was done in my institution by Campbell Rogers and compared the amount of emboli removed by the EPI device compared to that by the SAFER device, showing that the devices were equivalent once you controlled for the amount of particles and their enzyme elevations.

So we do start to see some connection between emboli and what is causing damage to the heart. The other thing about the SAFER trial was that the device that was used to remove particles, the PercuSurge device, compared to doing nothing at all, the main and only difference was that one

device removed particles and one didn't, and there was a 50 percent reduction in MI.

So I think that that is actually pretty solid proof that the emboli were measurable in their impact on the heart. It's about as solid as you can get, I think, from an 800-patient randomized trial.

So we do know that when using the heart as a surrogate, as an organ that has small vessels, like all organs do, that can be clogged up by emboli that have necrosis and damage as demonstrated by IIb/IIIa inhibitor trials and so on, that means something to the organ with a readily available measurable outcome, that we actually do prevent cell death by removing emboli, at least in that [inaudible].

So the next transition to say that actually capturing emboli in the body in general is not so much of a high-falluting notion or theory as something, as Dr. Marler mentioned earlier, like ECIC bypass or other things that are intuitive but maybe don't have as much connection.

So I think the evidence is growing, and there are lots of different venues now for investigations in which the notion of putting a

filter on a device is actually already intuitively being planned. For example, many carotid stents are now being packaged with filters where there is no attempt to look at the filter component part of safety; it just makes sense to put a filter on there, because emboli don't make any sense if they go to the brain, for example.

The same is starting to be done with studies in the rental area as well.

So I think there is a growing body of evidence that small emboli are not good for organs; in the heart, I think it is established; and as we start to look at other organs, that notion is starting to grow. And this trial was caught in the middle of that in having technology available for surgery using background information, like Dr. Kouchoukos had shown for years that this was a problem, and we were caught in the crosshairs of being able to demonstrate the emboli being removed with the growing idea that emboli can be measured in some organs but not in all organs, and potentially, if this trial were to be repeated in a year or two, maybe we would have much more sensitive measures. But that's kind of how we put that in perspective.

DR. KRUCOFF: I understand, and I take many of your points, Rick. On the coronary distal protection, as you well know, there is still ongoing dialogue about occlusive and nonocclusive and whether there are other elements besides particles. I don't want to intimate for a second that there is any proof that particles are good for anything.

I think the reverse side here, and particularly in a large vessel that feeds virtually every other vessel in the body, is what size of particles, how many of them, and at what cost is unfortunately where I think "caught in the middle" is probably a good phrase.

DR. TRACY: Dr. Laskey?

DR. LASKEY: When one gets to this end of the table, one had better be brief--or insightful. I'll be both.

[Laughter.]

Rick, you can't compare PercuSurge and IIb/IIIa inhibitors in the same breath. I mean, IIb/IIIa inhibitors don't do anything for large embolic goobers, yet they decrease the rate of necrosis.

So this is, I think, without being

dismissive, a rare outcome of a very prevalent disease. Atherosclerosis is diffuse, and without simplifying this any further, if you do diagnostic catheterization, you take a wire out of the body that has been in the body for 30 seconds, you are wiping of thrombi, you are wiping off platelets, you are wiping off clots--and yet the rate of stroke or embolization or other horrible things during cath is so acceptable that we don't even think about it. So we are not thinking about putting filters on our diagnostic caths, but those clots are there--let there be no debate about that--and it is a question of how sensitive the test is to look for them. So if you do scanning EM on your guidewires, you are going to find it.

And if we parlay that to where we are today, atherosclerosis in the ascending aorta is virtually present in 100 percent of the patients that you all operate on, yet the event rate--thank goodness--is acceptably low--1 to 2 percent, maybe 3 percent adverse embolic-type event rate. Now, it would be great if that were zero, but I don't think that's why we are here today. But I think we do need to be careful about signal and noise and reducing an event rate which agreeably is low but

could be lower.

So I am not entirely sure what we are all about here, and we are putting an instrument to the ascending aorta purportedly with the aim of collecting debris, but it is in there transiently, it is in there at a moment in time that you just sort of arbitrarily said is the moment of risk, and yet introducing the trocar [phonetic] into the ascending aorta could just as well release debris. Case-in-point--virtually every, single brachial arteriotomy I have ever done in a patient over 50 [inaudible] catheterization, you open the artery, and there is placque right there. I mean, it is a universally present disease in these patients, and yet the dread sequelae are fairly infrequent, and developing sensitive tools is critical--you have heard that; I don't need to repeat that. Assays for efficacy are sorely needed in this. And certainly, capturing the universe of the period of risk is critical. I think you need to be in there for the whole period at which the patient is at risk, and that includes from the moment you instrument or manipulate the aorta to the time that you go on or off bypass and give protamine.

Those are just more editorial-type

comments, but that is what we are all grappling with here, and I'm sure it has a lot to do with why we are not and may not ever, until we have developed an incredibly sensitive test, be able to demonstrate the efficacy of these tools.

But my one question to you is why 75 percent. Why did you pick that? Why didn't you pick 95 percent? Seventy-five percent is so little to my mind, given the prevalence, the universal prevalence, of this stuff in these aortas. Why not go for a higher figure?

DR. ALLEN: We certainly could have gone for a higher figure, and if it had been anything under 96.8, we would have met that higher figure. There isn't a historical background. We have never had the ability to place a filter in the ascending aorta before, so we don't know what those numbers are.

I think Dr. Edmunds early on was quite astute when he said the device isn't designed to capture all emboli, but is it better to have a device that captures some emboli or just not have the device at all, and we let those emboli go.

I guess that's the crux of the philosophical debate. I guess as a surgeon, having

put this device in over 100 patients and seen what it pulls out, I'd rather have something that I can use to pull out some of those emboli. You're right--I'd love to have a device that captured everything, but that's not what I have. I've got a device that captures a lot of emboli, and that has intuitively got to be good for the patient, and as you pointed out, the event rates that we are measuring are so small that to power a study to show pertinent and important reductions in those event rates would require such a huge study that from a practicality standpoint, it is not reasonable. So you design the trial to capture particles and show the device is safe. And I think that we have accomplished that by meeting both of our primary endpoints.

DR. KUNTZ: Just one statistical thing, too--you have to have a little bit of room for your [inaudible] about the number that you're trying to show so that you can demonstrate that the number you have has a lower battery that is above 75 percent.

DR. LASKEY: I understand that, Rick, but really, a device which is 75 percent efficient is nothing that I would want to fiddle around with.

I think that what we're talking about is efficiency on two levels, but certainly, the efficiency of retrieval--we have no idea what the efficiency of retrieval is. Is it 2 percent? Is it 20 percent? Is it close to something on the order of 90 percent?

Don't equate the measure of efficacy that you have here with the measure of efficiency of the device. We don't know how much of that stuff at risk of embolization is actually retrieved. Yes, 96 percent of your device have done so, but that's not the same as how much of the stuff which is at risk of embolizing is actually retrievable ergo how much do you lower the risk of embolization.

Dr. White, it's all yours.

DR. WHITE: I can't be insightful, so I will be brief.

[Laughter.]

I am intrigued by emboli protection. I am involved with emboli protection in multiple organs, as Rick knows, and I like the intuitive argument that I never saw an emboli that I liked. I think the problem is--and you guys probably know this better than I do, but for the rest of our panel members--as Dr. Laskey just said, taking five

emboli out of circulation is a great idea, but not if 500 get by. And I think there is a threshold at which we would decide that there is efficiency or efficacy in taking those--even partial prevention is better than no prevention--but there is a threshold where the partial prevention meets the road, and that is, I think--we have heard from multiple people who keep trying to get to this denominator.

The only thing I found in the whole pack--and tell me if I am wrong about this--it is under agency review for us; I don't know where you guys have it--it is under "Summary of FDA Methods" on page 3. At the very bottom, it says that you did an in vitro study with these 120-micron beads, and that your acceptance criterion was to capture 50 percent of those beads. Am I--I don't want to go faster than you can go--it is Number 5 in the Agency's summary. I don't know where it came from in the primary pack. Do they have the Agency summary?

DR. ZUCKERMAN: Yes. It is in Dr. Wentz' initial review.

DR. WHITE: On page 3--do you see what I am referring to? It is Number 5 at the bottom of

that page. And what it shows is that in vitro, I guess this is, if you said 50 percent was captured, and that was your goal, that was your acceptance rate. Is that what you set up?

MS. CHANG: That was the lower threshold.

DR. WHITE: So you would have been happy with a 50 percent capture rate?

MS. CHANG: These were polystyrene beads. We were testing the worst case. So they were literally like pinballs.

DR. WHITE: Yes.

MS. CHANG: Now, in the body, the particulates would be more sticky. So yes, we chose that lower threshold--this is based on initial bench-testing. Our values ranged from the large filters to small filters, so it was sometimes as high as 80, 90 percent.

DR. WHITE: Right. The design itself looks to me like it would be better than 50 percent. If I put that in a plastic tube and blew balls to it, just as you mentioned with the windsock, we ought to capture those balls. So when you start to talk about the failure mechanism, the reason that you would fail to capture them, is that because you are not getting uniform deployment of

the ring in the aorta? Are the balls sneaking around the ring? Why do you fail to capture a ball?

MS. CHANG: There is a little bit of a teeny gap right here, so again, on the smaller filter, this gap percentage is smaller. In a larger filter, it is a lower percentage. And it is just the way the filter is deployed, because again, there is a little bit of--

DR. WHITE: Because the next question I have for you that again goes to the clinical arena is could the surgeons judge the adequacy of the deployment. For example, the only experience I have like this is the EPI filter, which is a nitinol ring. And we image that radiologically and actually find a reasonable number of times that we have to adjust that filter to get it to actually oppose the wall; otherwise, it cants and tilts, and we don't have apposition.

Do you guys have any direct control over the apposition of this filter? Do you know if it is cocked, or do you know if it is--do you know what I mean--canted in one way?

DR. ALLEN: I understand what you are asking, and I think the answer to that is that

there is a tactile sense to the device that you can tell when it is certainly deployed, and when you are having problems with deployment, if you had a problem with deployment, that tactile sensation gives you that feedback, and you need to make adjustments.

DR. WHITE: But you don't actually look at the ring. You are not seeing it; it is going through the wall of the aorta.

DR. ALLEN: No.

DR. WHITE: And your ultrasound--Dr. Kouchoukos, when you image these with your imaging, can you actually see the ring on ultrasound?

DR. KOUCHOUKOS: It would be very difficult, because the probe is a 7-megahertz probe that sits on top of the aorta, and it would be impossible, really, to effectively image that area. And TEE doesn't give you a good image of that particular part of the aorta, as you well know.

DR. WHITE: And then--do you want to say something else?

DR. ALLEN: I just wanted to come back to your comment about do things go around. I think Jean talked about the small area at the top, but you all know when you look at femoral arteries or,

as surgeons, you look at the ascending aorta, that these aren't perfect manufactured tubes, particularly when you have disease in them--they have nooks and crannies and stalactites and stalagmites--and placing the device down in here, you wouldn't expect to get perfect apposition of the nitinol ring to the inside diameter of the vessel wall.

DR. WHITE: I agree, but that's the whole purpose of reaching the threshold where--your argument which you are trying to make it, which is that without measurable efficacy, less emboli are better than more emboli. And I would like to get comfortable that we are taking out most of the emboli, because taking out one out of 300 million--I wouldn't agree with your argument if you were taking out a vast minority of the emboli.

The other thing is in sizing--I notice that your device comes in 3 mm and 4 mm increments, and you size the aorta with a device that measures the outside diameter of the aorta. Have you looked at or measured any internal consistency among operators at being able to fit the aorta and get it right? Are you able to judge the right size of that aorta? How much do you miss? What is the

variability there?

DR. ALLEN: Actually, we make estimates of the thickness of the ascending aorta, and when you are sizing the device, you step down so that you take into account the internal diameter--

DR. WHITE: My question is is there any measurement of how accurate any given surgeon is, or between surgeons, at making the right choice for the filter in order to fit that aorta, because if you are going to have high-efficiency capture, you really want to be measuring very carefully, or at least be very on-the-money about the right size.

Do you have any measurement of that consistency or accuracy or the ability to correctly deploy the filter?

DR. ALLEN: I don't have specific measures where we measured how effective the surgeons were at measuring the device. The devices that you use to measure the size of the ascending aorta are graft-sizers that vascular and cardiac surgeons use every day, and to measure the size of the ascending aorta, it's not rocket science.

DR. WHITE: But with a 3 mm sensitivity, a little bit of mistakes make for incomplete loops, and again, if we are talking about that less emboli

are better than more emboli, I would want to know that you are accurately doing the best you can to screen all of those out.

DR. ALLEN: I can just tell you that as a surgeon, I think I do a pretty accurate job of using the vascular sizers to tell me what the size of the ascending aorta is and in choosing the appropriate filter size.

DR. WHITE: It would be an interesting experiment to actually do it in a model, even an animal model, and measure your emboli three different times or two different surgeons or take a couple of your fellows--you could tell us that, "Do you know what--we have five guys do it, and it's an easy thing to do; this thing fits no problem," or you could tell us that there is a tremendous amount of variability between surgeons and your ability to capture these or fit this device appropriately.

MS. CHANG: Dr. White, actually, I'm sorry--in Europe when we did our first cases in the early 1990s, we did that correlation, and that's how we came up with the aortic sizer. So we would have the surgeons--these were the first 20 or so cases--do the aortic sizers and also do MJ [phonetic], and they correlated.

DR. WHITE: How did you measure that?
MS. CHANG: I think they did imaging.
DR. WHITE: They imagined the loop?
MS. CHANG: The cross-section.
DR. WHITE: With what?
MS. CHANG: Epi-aortic.
DR. WHITE: With what--ultrasound?
MS. CHANG: Yes.
DR. WHITE: Okay.
The only other issue is that, again going back to the efficiency, the filters only filter everything bigger than they are, and that's a debate that we all have about distal protection devices. If you choose a filter which is nice to use, and you can have flow and all those things, you have to give up everything smaller than the 120 microns if that is the size you pick, or if you pick a smaller pore size, you get problems with that as well.
But that goes to the efficiency of fewer emboli, and that is that we really don't know that the big emboli are the problem. As you have shown in your graph, the smaller emboli block the smaller brain arteries. So you may be picking out the big chunks, and the little stuff is still causing a

problem, which is why I think we get back to if there is a threshold where taking emboli out is good, then we would like to get some measure of that efficacy. That is why I think just the rationale for me that taking out some emboli is better than no emboli is difficult to get enthusiastic about.

That's all I have.

DR. TRACY: I have just a couple of quick questions.

This study was specifically not done in people with very severe aortic disease, and yet it did show, whether these things are clinically relevant or not, more evidence for aortic disruption than not having a device deployed.

What is there that tells us that if we move into people with much more severe aortic disease that we won't have greater consequences of an increased number of aortic disruptions? Why would it be safe?

DR. ALLEN: If you recall the odds ratio table that I showed you at the very end of the slides, for example, in the higher-risk patients, there was a specific component there that looked at imaged placque what grade the aorta was, and there

was a correlation between grades of placque versus whether or not an EDS was occurring.

I can give you that assurance, that there didn't appear to be an increased incidence of EDS in patients who had worse aortas. What I can't come back to is that it is an assumption that more atheroembolism is generated in patients who have worse aortas--but I can't give you the denominator, as Dr. Laskey and Dr. White have both asked.

DR. TRACY: And the other question or comment I have is that there are other things that cause neurologic events. How do we know that the things that aren't getting by aren't the things that would be causing problems? I am struck by this lack of any kind of endpoint to look at that with.

DR. ALLEN: I think the whole flavor of particularly the last several questions illustrates the struggle that the panel has with the intuitive notion that particle removal is bad, but the study, because it is a safety equivalence study, doesn't show this dramatic reduction in events. And it relates, as we tried to go through, and it is--you want this device to be able to demonstrate a reduction of events, but as Dr. Laskey pointed out,

the events that fortunately occur with excellent cardiac surgical care today are not that high. So to power and design studies that can appropriately measure those events is very difficult.

I think the issue is that the composite events, or the events that comprise that composite, were chosen to look at the device as far as the safety standpoint, and that's how the study was powered. That's how the study was done, and as an investigator, I am pretty proud of how that study was done.

DR. KOUCHOUKOS: I think it's also important to recognize that the stroke rate in 80-year-old patients is not 2 percent or 3 percent. It is more like 8 or 10 percent. And the prevalence of significant renal dysfunction is also higher. We did not have a large percentage of our patients in this study, for obvious reasons, who were in that category, but one can assume that it might be possible to demonstrate efficacy in this high-risk group because of the higher prevalence of both of these major complications.

DR. TRACY: Dr. Aziz?

DR. AZIZ: The size of the filter in the heart-lung machine is usually about 20 microns.

The size of the pores here is about 120 microns, if I am right. In your testing and design before you came up with this, did you try filters with smaller pores?

MS. CHANG: Yes, we did. We looked at 85-micron pores, and the issue is the back-pressure, which then starts to create arterial resistance. So the 120 allows for basically almost virtually no pressure drop between the filter, and also to catch particulates of a size that-- again, Dr. Barbut and Yao [phonetic] did a study where they looked at embolic size with regard to neurologic outcomes, and there seemed to be a collection of larger sizes at about the 120 mark.

DR. AZIZ: This is has obviously been available in Europe since 1998 or so. Outside the group of patients that we have discussed today, is there a general feeling that in the older patients that are being done there--over 80--that there has been a clinical benefit?

DR. ALLEN: The short answer to that is yes, the European data would suggest that there is a risk reduction particularly in high-risk patients, but you'll note we haven't shown any of that data, because it is not randomized data. I

think it is not appropriate data, and I think you have to stand on the randomized control data, but you asked the question, and--

DR. AZIZ: And that's published, or was that just an impression?

DR. ALLEN: That's published data--European Journal of Cardiovascular and Thoracic Surgery.

DR. AZIZ: This is actually a question for future trials that involve neuro-protective sorts of mechanisms. Can the S-100 protein be used as a marker? Some people have done that for brain injury on cardiopulmonary bypass.

DR. ALLEN: I can't--Dr. Kouchoukos and Dr. Kuntz are both eager to answer that question.

DR. KUNTZ: And I'd love to hear Dr. Marler on that, because we would love to use something for carotid studies as well. I don't know if he knows about that.

DR. MARLER: No.

DR. KOUCHOUKOS: There is data in the cardiopulmonary literature, and Dr. Edmunds, who is the current editor of one of our journals, can probably address it. But it is a very insensitive marker in patients who are undergoing

cardiopulmonary bypass with neurologic injury. That's the short answer.

DR. EDMUNDS: The S-100 protein is a marker of neurologic injury, but it is also a marker of macrophage [inaudible] activation, and since these operations are all contaminated with field suction, reclaiming field blood, the marker is not a reliable index of neurologic injury.

DR. TRACY: Are there any other questions from the panel for the sponsor?

DR. MARLER: Could I ask one more question?

DR. TRACY: Yes.

DR. MARLER: I haven't heard much about the indications and the precautions, and we are asked about that. Could you walk me through your thinking on going from the selection criteria in the trial to what you are recommending as indications for use?

It seems to me that the trial selected patients at, at least neurologically, a lower risk of events, and yet, it seems you are actually intending to use this for a much broader range of patients. Is that correct, and could you walk me through at least some of the exclusion criteria to

explain why you wouldn't continue to apply them when it is actually used?

DR. ALLEN: I think from a practical standpoint, the device, except in aortas that couldn't be cross-clamped or that the surgeon chose not to cross-clamp, you are right, the device would probably be more broadly applied.

I think you do have an opportunity when you look at the subset of patients that were considered higher-risk that you saw some mitigating effect in those patients with the filter, so those patients were deriving a benefit.

It is an inference, and I don't draw superiority in those patients--I don't make that claim at all--but it does allow us to show that there is a subset of higher-risk patients whom we certainly didn't harm, and actually, some of the data suggests that we saw some benefit.

DR. MARLER: But I think you made reference that those patients at higher risk were excluded for obvious reasons from the trial, and they are not so obvious to me if you then intend to use the device in them.

DR. ALLEN: The patients--we specifically wanted to look at--when you design a trial for

safety, to demonstrate safety of a device, I don't choose patients who are going to have tons and tons of complications. If I want to demonstrate superiority, I choose a population that is going to have a lot of complications so I don't have to enroll as many patients, and I can demonstrate that.

So the trial, for all the reasons that we have discussed--and it is still a very large trial just to demonstrate that equivalency--was designed in that fashion.

There were patients, though, who were at moderate or high risk as measured by the Cleveland Clinic Score, 20 percent of our population, and in those patients, certainly the device was safe, and in that subset analysis, there may have been some benefit shown.

So I think surgeons are going to have to use their judgment as to whom they are going to use this in. The only patients from an aortic standpoint who were excluded were if you couldn't cross-clamp the ascending aorta. If they met inclusion and exclusion criteria, and you got to the operating room, and the patient unfortunately had a porcelain ascending aorta, those patients

weren't included.

So I think some of the precautions you are asking me to come to, clearly, if you can't put a clamp on the aorta, you are probably going to have to try to figure out some other method to revascularize these patients, and the filter isn't going to be appropriate in that population, because it is obviously attached to a cardiopulmonary bypass cannula.

DR. EDMUNDS: If I might just comment, I think the Higgins Score is almost irrelevant to this problem, because there are lots of ways to die, and the Higgins Score will be influenced by whether or not somebody has emphysematous [phonetic] lungs, and I can't see how this device is going to affect that--and a lot of other factors. I think that local factors are the ones that are relevant here--things that directly produce particulate emboli.

DR. ALLEN: I don't disagree with you, Dr. Edmunds.

DR. EDMUNDS: I hope not.

[Laughter.]

DR. TRACY: Dr. Krucoff?

DR. KRUCOFF: I just have one question,

really, to Dr. Allen and Dr. Kouchoukos, and accepting that this is not going to be a data-based answer. But if this device were approved and came on the market commercially, as two of the individuals who have obviously had their hands on it in human application more than anybody else, can you tell me just what ball park of your total clinical practice of open heart surgery you think you would use this thing in? In what percentage of patient would you actually pull this off the shelf and use it?

DR. KOUCHOUKOS: Based on what we know from epi-aortic scanning, as I showed you, we know that the prevalence of atherosclerosis begins to go up at age 60 or 65. The cut-off in this study was 60. I would consider using it in every patient over the age of 60.

In this study, we retrieved emboli in 96 percent of the patients. There is every expectation that as you apply this to older and older patients, we would retrieve more debris. So I would use it in any adult patient over the age of 60 undergoing a cardiac procedure.

DR. KRUCOFF: And again, Dr. Kouchoukos, in a very broad sense, is that 30 percent, 50

percent, 70 percent of your practice?

DR. KOUCHOUKOS: Well, it depends on an individual's practice, but in an average adult practice, that would probably encompass probably 85 to 90 percent of patients who have cardiac surgical procedures.

DR. KRUCOFF: Dr. Allen?

DR. ALLEN: I'm sure it's the same in your institutions. I don't have cardiologists referring me too many young, healthy patients anymore. Most of my patients are over the age of 64. The median age in my practice is 72.

I would agree with Dr. Kouchoukos. About 20 percent of my patient are done off-pump. I am not a huge advocate of off-pump, but I use it selectively in appropriate patients, so you can already take my number down to about 80 percent. I am going to use it in a lot of patients.

DR. KRUCOFF: So most of the patients in whom you would cannulate the aorta, you would use this device.

DR. ALLEN: Patients that I would put on cardiopulmonary bypass and cannulate the ascending aorta, I think the device is very safe, and the stuff you see on the filter, it's hard to say that

it's not a good thing to take these things out; so I would be using it pretty frequently.

DR. TRACY: It's hard to say it's not a good thing to take it out, but it's not easy to say that it is a good thing to take it out.

DR. ALLEN: Yes.

DR. TRACY: I mean, we have very little that says it is a good thing to take it out. I'd just like to make that point.

DR. ALLEN: Dr. Tracy, you are absolutely right, and I think that gets back to the whole issue that it is a safety study and not an efficacy study.

DR. TRACY: Right.

Are there any other questions from the panel at this point?

[No response.]

DR. TRACY: If not, we'll take a 15-minute break and then reconvene.

[Break.]

DR. TRACY: If everybody would take their seats, we can reconvene.

There have been a number of questions regarding the efficiency of this device at collecting whatever "goobers" it is collecting, and

I believe the sponsor may have some additional information that might help us understand the efficiency of this device.

MS. CHANG: Yes. We just got our bench test results from California, and the average in the bench test is 80 to 90 percent.

DR. WHITE: Is that the experiment with the 120-micron beads?

MS. CHANG: Yes--the pinballs flying all over.

DR. TRACY: And there were no studies done with something that was more similar to atheromatous or to blood clots; is that correct?

MS. CHANG: Yes.

DR. TRACY: All right. At this point, we'll start going through the questions that were posed to us by the FDA.

Questions for the Panel

DR. TRACY: The first question: The primary safety endpoint for this study was a composite of seven adverse clinical events detailed on this slide. The median followup was 7 days. Some facts from the study are: The observed overall composite event rates were 17.1 percent in the EMBOL-X arm and 18.9 percent in the control;

the composite event rate for the EMBOL-X arm was shown to be equivalent or not different from that in the control; also as specified in the protocol, a separate test for a lower event rate in the EMBOL-X arm was not statistically significant; the EMBOL-X arm demonstrated a significantly higher incidence of aortic endothelial injury--9.2 percent versus 2.0 percent. Although these patients did not appear to have any short-term clinical sequelae resulting from these injuries, long-term effects are unknown.

So the first question posed to us is: "Do these data support the safety of the EMBOL-X intra-aortic filter?"

I am supposed to summarize the discussion, and I really have no idea. I think in terms of being equivalent, if that is equivalent to doing nothing, then, I suppose it is equivalent to doing nothing. I really don't know how to answer that question. I'll have to ask the other panel members if they can be more articulate than I on this question.

DR. KRUCOFF: Isn't safety and issue of doing harm? I think from what I heard discussed, other than the scanning finding of the "ding" or

whatever we are calling the little flap of tissue, which it seemed pretty unclear is related to any kind of clinical sequelae, it sounded like there was reasonable information to support that no harm was being done. The non-inferiority statistic actually also, to my understanding--and David, maybe you can chime in--implies that at least no harm is being done.

DR. DeMETS: Yes. My assessment of that would be that it certainly met the criteria that were established for the clinical delta that you were after, and moreover, the rates are actually lower in the treatment arm; overall, the composite is lower; and when you examine the individual components, most of them are at least in the direction--a few are in the wrong direction, but just by a little bit. So we would like to have more data on that, of course, but this is what you have.

So for the issue of safety within the criteria that were set up, I think they have met those goals.

DR. TRACY: Yes. I guess the thing that I'm struggling with is that I question whether this was an appropriate safety endpoint, but it was what

was predetermined to be the endpoint of the study.

Bram?

DR. ZUCKERMAN: Right. Dr. Tracy, I think multiple people have commented that in the year 2002, they might design a different-type trial, but we have to appreciate how FDA and the sponsor designed the safety primary endpoint when the trial was first designed. And I believe safety was really designed the way Dr. DeMets just summarized. They met the delta. The trends were in the right direction. And our third concern, which the panel has commented on, was that the aortic disruptions did not have significant clinical sequelae, and if that is the agreement of this panel, then, for our purposes, it has met a safety definition.

DR. TRACY: I think it has met it in the patients that it was tested in. I don't think you can extrapolate beyond the patients who were tested. I don't think there are data that would support expanding into a different group of people, for example, people with greater degrees of aortic disease. There are no data that support that.

DR. ZUCKERMAN: And I am glad that you mention that, because multiple panelists asked about that this morning, and that question of

labeling is a critical one that we will get to in Question 4.

DR. EDMUNDS: Yes, but this was a random sample of a population of patients that has been well-characterized and defined. The mean age was 71. So I do think that if statistics apply to anything, they apply to a set of patients that fit these descriptors.

DR. TRACY: It applies to the patients that were included in this study. It doesn't apply to another type of patient. So I would agree with you. But that has--

DR. EDMUNDS: Other type of patients.

DR. TRACY: Right--that were not studied.

Are there any other comments regarding this first question?

[No response.]

DR. TRACY: If not, we'll move to Question 2.

"The primary effectiveness endpoint in this trial was to demonstrate that 75 percent of the devices would capture at least one particle during elective CABG or single-valve procedures. This was demonstrated in the study. There was no demonstrated reduction in any category of clinical

adverse event in this well-controlled patient trial."

"Please address the following concerns: 1) Can this method of embolic entrapment, from this study or elsewhere, be extrapolated to clinical efficacy?"

I think that the answer to that is that we probably cannot extrapolate beyond what data we have. We do see that it is efficiency in retrieving material from patients undergoing surgery. We don't have data that would support clinical advantage to that. We don't have data that it is harmful to retrieve this material. But I would be cautious about extrapolating on the basis of intuition.

DR. LASKEY: I'm not sure that we know it is efficient. We know that it does. We don't know the efficiency. So perhaps it's best just not to use that term.

DR. WHITE: The confusion comes from the fact that 90 percent of the patients had some; so I think that's where you say that a high rate of recovery. But the number of total emboli that was recovered is unknown, and I tend to think of that as the efficiency of the filter, so it is an

unknown efficiency rate.

DR. TRACY: Okay. Good point.

Are there any other comments on that particular bullet?

DR. KRUCOFF: Well, there are sort of two parts--clinical efficacy and efficiency. On clinical efficacy, it would seem like we were pretty consistently clear there is no demonstration of an obvious relationship other than thinking that emboli are bad. There is no relationship in the data to clinical efficacy.

And the second part is really about effectiveness or efficiency of thrombi, and there, I think we have, as Chris said, the denominator issues.

DR. TRACY: And the second part: "Do these data support the effectiveness of the EMBOL-X intra-aortic filter?"

I think you are hearing comments on that that we don't know how much was missed that was not captured. There is no way to know what was not captured by the device.

DR. FERGUSON: Does the fact that it captures a known quantity that we know about give them a plus? I think it does.

DR. TRACY: I think the problem again is that we don't know what it doesn't capture. There is no bench data that tells us exactly what it doesn't capture with something that would be bioequivalent to human atheromatous material or clot.

We know that it captures something, but we don't know if there is 1,000 times or one time or 10 times as much that is getting past the filter.

DR. FERGUSON: But you are posing that as a negative, and what I am looking at is the positive, which is that it captures a known quantity that we know it captures over the non-use of the filter.

DR. EDMUNDS: Yes--you have distorted the question.

DR. FERGUSON: No.

DR. MARLER: I don't think he has. My concern is that my common sense and intuition tell me that using the word "effectiveness" and not meaning "clinical benefit" is distorting the question. Whether the filter pulls back objects or not, I don't think there is any question.

DR. TRACY: Maybe the FDA can clarify what they are actually asking us here.

DR. ZUCKERMAN: In an ideal world, certainly, we would have liked to have been able to say yes to clinical efficacy; it makes it a much easier decision for everyone concerned. But I think everyone agrees that those aren't the data that we have in front of us, so what we are looking for is expert clinical opinion. For example, the fact that we have this device, this tool, that can be used in cardiac surgery to take out a certain number of particles, for the cardiac surgeons on the panel, is that an effective device? We won't be able to give you the denominator, but we would like your clinical impression.

Certainly for those who don't do this procedure every day, we may have a different impression, but we are interested especially in the cardiac surgical perspective.

DR. EDMUNDS: Well, the term "clinical efficacy" is a very ambiguous term. It's a bad term. Does this method of embolic entrapment remove particulate emboli from the circulation? That is unambiguous. That's what the question should be.

The second question is does it have clinical effectiveness, if that's what you want to

ask. But you have got to have an unambiguous question.

DR. ZUCKERMAN: Okay, then, how would you answer those two questions?

DR. EDMUNDS: You would like me to answer?

DR. ZUCKERMAN: Yes.

DR. EDMUNDS: I'd be delighted to answer. Do you want it in half an hour or less?

DR. ZUCKERMAN: Yes.

DR. EDMUNDS: It does remove emboli, and they have not shown any clinical effectiveness in this study.

DR. FERGUSON: I would agree with that. I don't think we have data to support the clinical effectiveness. They have said that, and we have said it here, so that's easy to answer.

But I do think that we still have to say that in the sum total of taking care of patients in the operating room, anything that you can do where you can prove that you are taking out this material, but anything you can do like putting a filter in the arterial pressure line of the heart-lung machine, and we see the material that is trapped in that filter, we know that that's a good thing for the patient. And I view this as the same

sort of thing.
DR. ZUCKERMAN: And, Dr. Aziz, do we have consensus there?
DR. AZIZ: Yes, I think I would agree with the other two surgical members of the team.
DR. TRACY: Okay. So I think you have heard the spectrum of answers on that. We don't know how much is left behind, but it's a good thing to take away something.
DR. WHITE: Do you want to hear the other side of that argument?
DR. TRACY: Absolutely. Dr. White?
DR. WHITE: I think that that is not clear. I could put anything into this patient's body and have a few bits stick to it and say, "Look, I got one." Is it a tool that takes out emboli? Yes--I got one out of 150,000 emboli.
My problem is--I won't argue that 97 percent of these patients had emboli removed--what I am concerned about is that I have no idea whether that is doing the patient any good. I think that I would feel much more happy with partial capture and a clinical benefit than to support the efficacy of a tool that may not have any benefit.
So the question then is are we denying the

surgeons a tool that they might want to use. I think that's a much more difficult question. But I don't want anybody to get confused that I have some understanding that the tool that removes some benefits is something that I could say is a good thing to use in the next patient that has bypass. I think that's the difference between that and the bypass filter. The bypass filter is very small; it captures lots of bits. The question of efficacy there is much more easily satisfied, because you can look at the other side of the filter and see what it misses. What these guys can't tell us is what is on the other side of the filter, what is being missed--plus the filter is partially filterable, and there is disease distal to the filter that causes these events, both renal and neurologic, multifactorial disease. So I think we don't have a very good handle on this.

DR. TRACY: I think these are very difficult questions to answer, and the problems are the difference between clinical efficacy, and I think the answer is pretty clear on that part that we don't have demonstrate of clinical efficacy, and the problem with effectiveness of the device--it removes something, and the surgical feeling is that

it is a good thing to remove something, and the other side of the coin is that we don't know if it is removing one one-thousandth or 90 percent of what is there available to be retrieved. That is the ambiguity that I think--

DR. LASKEY: Can't we do better than that? It is so disingenuous to let us go on the record as saying that taking something out is a good thing. It's just so disingenuous, it makes me very uncomfortable.

Suppressing PVCs is a good thing. It also kills people.

I just can't accept that. Can we change the language? Taking something out is a good thing--no.

DR. EDMUNDS: Warren, we have got to put this problem in the context that it really is. Embolization to the brain has been known since Lee's paper in 1960. It has been a huge problem in cardiothoracic surgery with bypass since that time.

The improvements that we made that allow us to have the cognitive deficits that we have today are small, incremental improvements--heparin dosage, antifibrinalitics, protenine--all those sorts of things. It is going to be incremental.

This is just a little baby step, perhaps, but it is a step in the right direction because you are dragging out some garbage.

I think you have to look at it in that context. That means that there is a lot of garbage still in there. We know that. But we are going to be taking it out spoonful-by-spoonful. That's what it has been for the last 42 years.

DR. TRACY: I have the feeling there is not going to be consensus on this.

DR. MARLER: No. I think that the question about whether it is good or not to remove the emboli in a way is kind of independent of this discussion. I mean, that could be answered by different studies or looking at the literature and forming an opinion that way, which we really have not done.

I thought we were looking at the results of a particular trial.

DR. TRACY: If we remove the question of whether it is good or not, then I think the answer becomes even more difficult, because if we don't assume that there may be value to removing it, we have an unknown percentage of something that is being removed, and it becomes even more difficult

to answer the second bullet.

So I think I respect the surgical opinion that removal of material that would otherwise have gone somewhere probably is a good thing, although we do not have that clinical efficacy answer.

It is unfortunate that there is not a better endpoint in this study to look at. I'm not sure we're going to get much farther than where we are with this question.

DR. KRUCOFF: I'll just make one comment and probably end up having to change specialties, because I actually lean toward the surgical group on this one.

I think it would concern me if we felt that these little intimal "dings" or that some other significant safety issue or that some technical element that really made you redo or do differently the basic procedure of cannulating the aorta were a part of this device. Then I would feel very conservative about all the issues that have been so much discussed, about whether pulling grunge out of the [inaudible] meant anything.

I guess, based on our consensus on the first point, if there is really no significant safety issue--and my understanding of the

discussion this morning, including all of us surgeons on both sides of the table, is that you put this thing in, you cannulate the aorta the same way you would for another purpose, and you basically slide the filter in with a pretty straightforward--essentially, with no real technical change from how you would do a routine open heart procedure--then, if debris is bad, and you are pulling it out, is that the first spoonful--it sounds to me like the surgeons from both sides of the table feel like it probably is. And it is very clear that we aren't going to see any answer to that question in the dataset. But if there is not a significant safety issue, then, to me, a lot of the judgment about whether or not to use this probably ought to come not from the panel but from a community of surgeons who do this in live patients, and the only way they can do that is if it is available.

DR. TRACY: Other comments on this question?

[No response.]

DR. TRACY: If not, we'll move to Question 3.

"Do the study data support an appropriate

risk/benefit profile?"

I think you have--I'm not sure what the question is, really.

DR. ZUCKERMAN: Okay. Dr. Krucoff just gave an answer to the question. He is looking at the data in this study as well as general experience, literature, et cetera, to try to come up with a risk/benefit profile which he judges to be positive.

We are asking for other comments. At the end of the day, one needs to cut to the chase. Is there enough data within this study and external data to agree with Dr. Krucoff's comments?

DR. TRACY: I think you're going to hear the same kind of debate back and forth among the panel members. I think within the confines of the type of patient who was involved in this particular study, Dr. Krucoff's answer probably is the correct answer. But I would caution again not to extrapolate too widely, and I am having the sense that there would be wide extrapolation if the device were clinically available.

DR. MARLER: I guess I can say that it's hard to compute a risk-benefit when you have no indication of any benefit. I am extremely cautious

about, quote, "approving," whatever that means, something for which there is no evidence of any benefit. And there is some risk--we have discussed it--and there were a lot of questions about whom it is going to be applied in.

So I would say that you can't say that the study data support a risk-benefit profile because they don't support any benefit.

DR. EDMUNDS: I think I can disagree with that. It does not support any clinically demonstrable benefit except that it removes a filter full of garbage, and that's a benefit.

DR. TRACY: Accepting that on, basically--at this point, we have been asked to accept that on intuition, and I have a hard time accepting that on the basis of intuition, because we still struggle with not knowing what got by. So it is very difficult, I agree.

DR. WHITE: The problem is it only takes one piece to cause a stroke. You can get an endpoint with one piece. That is why it is hard to know that if you got 60 percent of them, there is a clinical benefit associated with that, when it only takes one to cause an endpoint.

DR. EDMUNDS: I am just really frustrated.

For 42 years, we have been doing open heart surgery, and we have known that we have been circulating emboli. We're going to do it tomorrow, with or without the filter, circulating emboli. So there is no argument that there are no more emboli going to circulate if you use this device. There are going to be lots, but there are going to be less. The amount less is what is on the filter. That's the benefit. It is not a clinically demonstrable benefit.

They didn't measure clinical benefit in this study. They didn't say they measured it, they didn't intend to measure it. We can't hold them to that standard.

DR. TRACY: I think it's a little more than that. I think it's the whole issue of what is not known about what gets by. That's a very, I think, unknowable thing. There is something appealing about removing debris, but we don't know how much is being removed.

Dr. Laskey?

DR. LASKEY: I think what Hank says is absolutely on the money. I would agree with it 100 percent. It is just unfortunate that most people when they hear "risk-benefit" think about clinical

benefit. They think about the risk of harm, and they think about the risk of clinical benefit.

So perhaps again, the language could be softened here somewhat. But "benefit" here needs to be strictly qualified that this is not an artifactual benefit, but it is a benefit in terms of the study, which is strictly defined as catching stuff on the filter. But it is not a clinical benefit. When people see "risk-benefit," that's what they think of.

DR. WHITE: Do you need to consider the potential risks because you didn't measure a clinical risk in these patients; are there other theoretical or potential risks? We had a lot of discussion about air. We had discussion about disruptions, use in people with more sick aortas.

If we are going to hypothesize about a possible benefit, should we hypothesize about how potentially dangerous this could be if the device were misused?

DR. LASKEY: Thank you, Chris.

One point I wanted to mention is that we don't know that these disruptions are the triponine [phonetic] of cardiac surgery. We didn't know about triponine until we started looking at these

very, very subtle markers of injury. I'm not sure we know--none of us wants to believe that they are bad, but they may be, and it may be a very subtle marker of injury that we just don't have a handle on, just like triponine was in the early days.

So I wouldn't dismiss it, and I would certainly keep it in the mix. I agree with you.

DR. TRACY: Dr. Ferguson?

DR. FERGUSON: I agree totally with the concept that this question is bad in the sense that "risk-benefit" does convey something other than what we did.

I think we have all agreed that the risk is no greater than the control in this, and the benefit is that it takes out some clot, which we know is bad. And that's a better way to put it, I think, than the way it is written.

DR. TRACY: Are there any other comments on this question?

[No response.]

DR. TRACY: Does that satisfy your question, Dr. Zuckerman?

DR. ZUCKERMAN: Well, I think it is important for the record to know if the other two cardiac surgeons agree with Dr. Ferguson's last

statement, that if we more precisely define what we are trying to get at here, if they would agree.

DR. EDMUNDS: Well, we are splitting hairs, and I have on my loop, so that first of all, it is not clots that tare being taken out. It is atherosclerotic debris, principally. And I don't think that we have demonstrated clinical benefit, but we have demonstrated a benefit, and we have discussed that.

There is a risk. The risk is exceedingly low. It is the EDS risk. And while it isn't zero, it is the number next to zero.

DR. AZIZ: I think--how can I put it--clearly, I think that those two things are both in a sense true, and I hope they are connected in the sense that we do believe that removing clot will give us reduced brain injury, and I agree with what Chris is saying that we don't know how much is getting through on the other hand, and you really don't need to have a lot going through.

But to sort of crystallize it, I think the wording of this statement is a little fuzzy. I think that what one should say is that clearly, this device has some risks, but at the same time, it reduces some other risks--namely, the risks

associated with the lot.

So I think I would agree with what Dr. Ferguson is saying.

DR. TRACY: Okay. We'll move on, then, to the fourth question.

We are being asked in this question to review the labeling. "The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding product labeling: Do the Indications for Use adequately define the patient population studied? For example, should the patient population receiving this device be limited to the same patient population utilized in the study. For example, non-emergent; patients over the age of 60; first-time isolated valve or CABG patients."

We'll take that first piece first. I think that there may be some sense that it would be applicable in other patient populations, but we have pretty scanty information as it stands, and I would be very cautious about expanding beyond the population that was studied in this protocol.

DR. AZIZ: Well, I don't know quite how to take that, because we know that certain patients are at higher risk of getting this sort of problem, particularly the guys who are over 85, and although that didn't form a large percentage of the cohort, I think it comes back to what happened in a sense yesterday. Although you may say that, I think that in clinical practice, if I wanted to use this device, I would probably want to use it in a patient group that I know is at increased risk of having a neurological event.

So no matter what we say, I think that in clinical reality, you probably would target the higher-risk patient anyway.

DR. TRACY: Yes. My only point is not to extend it to the porcelain aortas or beyond the scope of this particular study. There did seem to be a group in whom there might be greater benefit, and that was the higher-risk patient population within this study. I think we have no data beyond this patient population, which did include some higher-risk but not the extraordinarily high-risk patients.

I think you have what you have.

DR. EDMUNDS: Dr. Tracy, I would like to

take two words or two phrases out of that. I would like to take "non-emergent" and "first-time" out of that statement. Otherwise I can live with it. But there is no sense in handicapping the surgeons when they are doing more difficult cases who are otherwise over 60 and at risk of this problem.

DR. TRACY: Do either of the other surgeons have any comments?

DR. FERGUSON: We're talking about labeling here, and the question to me would be--and you have a good point, I think, Cynthia--or what I am wrestling with is should the labeling say that this device was tested under these conditions, and put those conditions in, which would work for the FDA and work for our consciences and so forth. Now, the way the device is going to be used is of concern to us, but it is of no concern, because it is going to be used--Dr. Kouchoukos already said the ones he is going to define and use--

DR. ZUCKERMAN: Maybe we can have a time-out here and talk briefly about what we are getting at in this question.

Certainly the agency doesn't regulate the practice of medicine, and if the device is approved, there will be surgeons who will use it as

they want to. But what we are talking about today is truthful and accurate labeling in an indications statement, and then, part and parcel, we traditionally describe the clinical trial that was performed in the Clinical Trials section.

I guess the main question that FDA has is when we look at the indications and intended use, it says that "The EMBOL-X aortic filter is indicated for us with the EMBOL-X aortic cannula in cardiac surgery procedures to contain and remove particulate emboli."

Based on the data that we discussed this morning, should there be additional qualifiers that better describe who was actually studied?

DR. TRACY: You can refer to that in the "Proposed Labeling" section; page 2 of 10 at the top has the proposed indications for intended use. And then, on page 4 of 10, it begins the description of the patient population.

DR. FERGUSON: What was the first reference?

DR. TRACY: It is in the section titled, "Proposed Labeling," page 2 of 10, down at the bottom. And it is at the very top, Number 2, and it is exactly what Dr. Zuckerman said.

"The EMBOL-X aortic filter is indicated for use with the EMBOL-X aortic cannula in cardiac surgery procedures to contain or remove particulate emboli."

And the question is do you then add the phraseology "in patients over the age of 60 who are undergoing first-time surgery for isolated valve or CABG"--I think that's the question, or is it adequate on page 4 to state the description of the patient population that was studied.

My instinct would be that in general, we state the indication, unless there is a particular reason to put a qualification on it, and usually put those caveats in in the description of the patient population. I'm not sure that it is critical to put that up front in the labeling, but I think it has to be somehow there that that is the patient population that was studied.

DR. MARLER: So we are talking about indications now?

DR. TRACY: Right.

DR. MARLER: I guess it depends on whether you think your recommendations need to be driven by data, or not. I would personally be concerned, because my knowledge is that if you exclude

patients who have had prior stroke in the study, you are very unlikely to get any estimate of the risk of stroke from a procedure, because that's one of the highest-risk groups of patients.

And we heard from the sponsor that the reason this population was chosen--at least, my interpretation of the response--was because they wanted to select a group of patients in whom it was safe, or most likely to be safe.

So I think to take it beyond that without any data to support it would be against my understanding of what we are doing here today, which should be driven by data from the study that we are presented.

DR. TRACY: So are you supporting adding the phrases in "Indications and Intended Use," "non-emergent; patients over age 60; first-time isolated valve or CABG patients"? Would you propose putting that in the indications statement?

DR. MARLER: Well, because on some of those exclusion criteria, I don't have the expertise to interpret them, I would certainly think that you are changing the game if you include patients who had prior stroke or carotid stenosis. I don't know how the filter could possibly relate

to that.

What I would say is that I think each of the exclusions need to be discussed carefully in terms of whether there is any indication that it is also safe in those patients.

DR. TRACY: Maybe a more detailed description of the exclusion criteria would be helpful in there. That doesn't seem to be particularly well-detailed in the proposed labeling. And I think perhaps in the section entitled "Indications and Intended Use," if there were some reference specifically to "Please see below for specific patient population inclusion and exclusion criteria" and a statement that the device was tested in these patients only, would be appropriate.

DR. FERGUSON: Yes. As data?

DR. MARLER: Right--whatever. I just think that if you make the decision that intuition is going to drive this whole process, there is almost no purpose to even do the trial beyond the first few number of patients where you show it catches some emboli.

So I think that the basis of approval for anything should have to do with data that show that

it is safe and effective.

DR. TRACY: Okay?

DR. ZUCKERMAN: Well, there are still a lot of question marks for these other potential patient populations. Sometimes, what we do in our labeling is after the "Clinical Trials" section, in what would be before Section 8, we have a discussion of individual patient considerations where we could talk about some of these sub-populations and the lack of known data right now.

Do you think that it would be appropriate to add that section?

DR. TRACY: I think that that would perhaps be helpful to somehow, if you can, capture some of the questions about the other patient populations. I think that would be appropriate, and reference to that in the original Number 2, "Indications and Intended Use."

DR. EDMUNDS: I think it would be more concise just to say what the study was done on, and that is what is up there, and then put that in as data, and then put a disclaimer that the manufacturer does not extrapolate these data to anybody. They probably wouldn't say it just that

way.

[Laughter.]

DR. TRACY: Let's move on to the other bullets, and maybe it will help us clarify.

The second bullet is: " Are there any other restrictions that should be placed on the patient population receiving this device?" And I guess that means in terms of contraindications. I think rather than contraindications, simply stating that other patient populations were not studied would be the more appropriate way of stating it.

DR. FERGUSON: Contraindications are in the next bullet.

DR. TRACY: Right.

DR. KRUCOFF: Yes, and one that has come up that I didn't see in their labeling is the porcelain aorta as at least one morphologic descriptor that has come up a couple of times today that at least in my version is not specifically listed as someone who would probably not want to--I wonder, is there a broader range, or is it worth saying the obvious, which is that in patients in whom you would simply not want to cannulate the aorta, those are patients who are obviously not candidates for this?

DR. TRACY: The next section is, "Based on the clinical experience, should there be additional Contraindications, Warnings, and Precautions for the use of the EMBOL-X intra-aortic filter?"

DR. MARLER: I want to back up a little bit. On these indications and contraindications, aren't we more deciding not what an individual physician can do in his or her practice, but what the company can advertise as what the FDA has looked at and approved as an indication, presumably, following the meaning of FDA approval, that it is driven by data and good evidence?

MR. MORTON: Madam Chair, a couple of points, not to supersede Dr. Zuckerman.

DR. TRACY: Yes.

MR. MORTON: There is a difference between approving and clearing a 510(k), and that's what the FDA action will be; it will be a clearance. So the sponsor or the manufacturer will represent the device as "cleared," not as "approved," and that is significantly different.

Additionally, there is a tremendous difference in the regulatory burden on indications and changing indications once those are locked into a clearance. It requires data and could even

require another 510(k).

DR. MARLER: But the impact of the indications is primarily the way the product can be advertised and sold, not the way it is used by the physician; is that correct?

MR. MORTON: That is a practice of medicine issue; correct.

DR. ZUCKERMAN: Okay, but the point that we are trying to get at is what is a truthful way to describe the dataset that has been discussed here and other external data that is potentially of importance, Dr. Marler. So that the indications statement doesn't need to necessarily follow, dot by dot, the clinical trial guidelines if it is reasonable to extrapolate farther. That is where we need your help; it may not be.

DR. TRACY: Yes. I think it is very hard to extrapolate the way this particular study is constructed. It is hard to extrapolate, to expand on the indications. I think that the indications as stated in the--I'm not sure I would want to be more restrictive than what is stated here, other than to say that somewhere in the subsequent body, there has to be a statement of exactly who was studied and exactly who was not included. I think

the exclusion criteria have to be more clearly stated than they are in the current proposed labeling.

As far as placing additional restrictions, I don't think we need to place additional restrictions beyond clearly reiterating what was studied and what was not studied.

Dr. Pina?

DR. PINA: Let me go beyond the inclusion criteria. I would like to see a table with the baseline values of the patients. They were over the age of 60, but the age was up there, so I think that whomever is going to use this needs to see the mean values of the population that was actually studied. And it can be very simple--age, gender, type of surgery, even number of vessels involved. That information should be available. But that's a descriptor that I think a surgeon needs to look at to make a decision about whether they want to use this or not.

It's not just the inclusion criteria; it is what the data actually are.

DR. TRACY: So that is there in paragraph 4 on page 4 of 10 and perhaps would benefit from expanding that into a more inclusive table.

DR. MARLER: And I guess I would want to add that I thought I pretty clear asked for an explanation of how to extrapolate, and I did not hear anything except that emboli are bad.

DR. EDMUNDS: I don't think we can extrapolate, and I don't think we can say the negatives, either, because the negative list will be long. You start out with dissecting aneurysms, marfands [phonetic], airlos-dolos [phonetic], Siamese twins--you can keep going in an endless list. I think we have got to just stick to what this trial was. The use of this product is based on the demonstration that this filter captures embolic material when used in these patients, and that's where I would recommend that you stop, because that's all the data that we have.

DR. LASKEY: And it is exceedingly difficult to stretch things beyond the equivalence. If we had evidence of benefit, it could conceivably stretch this to another sample, but with equivalence, that's a long way.

DR. KRUCOFF: I would even amplify that to emphasize that since part of what I think makes this whole consideration reasonable is the absence of safety concerns, pushing the envelope in

directions to new, untested populations, I think whether you encounter safety issues would be an important question that would be outside of this discussion.

DR. ZUCKERMAN: Good. So you know what the present indications statement reads. How do you make it in a concise fashion more applicable to the data that have been presented?

DR. TRACY: I think you have to simply state, "See patient selection criteria for patients involved in this protocol." I think you have to refer to some other section. Otherwise, you end up with a 15-paragraph--you have to refer to other areas in the labeling and then perhaps a statement that this device simply was not tested in other patient populations.

DR. ZUCKERMAN: Okay. Another option that we sometimes use--the one that you have suggested is just to put, "(See Clinical Trials section)" in parentheses. Another option that we sometimes use is to indicate some key clinical parameters right in the indications statement of which there aren't any right now.

Are there any that are real show-stoppers that should be up front?

DR. TRACY: I think they are all relevant, and I think you just have to refer to who was involved in this study and specifically who was not involved in this study.

Dr. Ferguson?

DR. FERGUSON: Are we through with that? I want to bring up another point.

DR. TRACY: Yes.

DR. FERGUSON: I think it belongs here; maybe not. That is that as I read through these--and correct me if I am wrong--I see nothing at all in the deployment and use of the device that indicates that you should use imaging as a guide. I know that you don't need it to put the instrument in, but is there any reason--I am just bringing it up as a question, because half of the patients had either TEE or the epiaortic.

I would like to have some discussion about whether that should be somehow included here.

MS. WENTZ: That's actually the last part of the question.

DR. FERGUSON: Oh, okay. I jumped the gun. It's not in there now; right?

DR. KRUCOFF: My understanding from the comments from the investigators was that it just

would not be conceivably or technically feasible to do that on a routine basis.

DR. TRACY: I think their point on the TEE was that you wouldn't pick up these small disruptions.

DR. FERGUSON: TEE isn't available for everybody.

DR. TRACY: It is available, but it may not pick up these small disruptions that we don't know, as Dr. Laskey said, what the clinical relevance of these are. We know that they are occurring at a higher rate, and short-term, we don't see any increased adverse outcome related to it.

DR. FERGUSON: Excuse me. That jumps the point. I'm not talking about that. I was referring to the fact that it is very useful when you are getting ready to put an aortic cannula in, as Dr. Kouchoukos has done in monumental studies, it is very useful to have some sort of visualization of the arteriosclerotic aorta before you put the cannula in. I would like to have some discussion of that.

DR. EDMUNDS: Well, that adds a little bit of a burden and delays the operation by about 10

minutes, because first of all, you have to get the probe sterilized, and then you have to find an anesthetist who knows where it is, and it take about 10 minutes to do the study.

DR. FERGUSON: And probably if you do that, and you put the cannula in a spot that is not arteriosclerotic, you are probably doing the patient more good maybe even than the filter. That's my point.

DR. PINA: Dr. Tracy, let me go back to Dr. Zuckerman's point, because I don't think we answered that first statement for you.

In your statement of indications, I think you can very easily say, just like it says now, for cardiac surgical procedures that are non-emergent and in patients over the age of 60, for either bypass or valve surgery--you can say all of those indications in one sentence, and that will describe generally the population, and then say "Refer to Table such-and-such."

DR. TRACY: I think you are going to have some argument from your surgical colleagues that that is appropriate to limit the surgeons' ability to do this in emergency cases. So that was why I was holding back from making that particular

statement. I think it is important to say that that is the patient population that was involved, but I don't know that I would put that pu front.

DR. PINA: Yes, but the FDA will not regulate medical practice. They are going to do whatever they want anyway. The surgeons are going to use it any way they want, but I think the truth-in-labeling has to be the population that was studied. And the surgeons will make their decisions clinically, as we have always done with everything we do.

DR. TRACY: I think that is going beyond the scope of--I think to put that in there in the indications creates some liability issues that I would rather not open up to. I think we need to have it very clear that this is the patient population that was studied, and these are the people who were excluded. I'm not sure that it belongs as an additional sentence in the indications for usage.

DR. EDMUNDS: I agree with you. I think that's the data-supported course.

DR. TRACY: But the reference needs to be there.

Just to try to get through these other

issues, "Are there any other restrictions that should be placed on the patient population receiving this device?"

No, there are no other--I cannot think of any other restrictions that we have discussed here that need to be placed. Again, it has got to be clear who was excluded from the patient population.

And finally, on the third bullet of this question, "Should there be additional Contraindications, Warnings, and Precautions for the use of the EMBOL-X intra-aortic filter?"

I think, with the exception of the porcelain aorta, which has come up a couple of times, the contraindications as stated are fair, and I think somewhere, the idea of the porcelain aorta has to come up, either as a warning or as a precaution.

Dr. Krucoff?

DR. KRUCOFF: I have a question, and there may not be a precedent to make this helpful, but I wonder if it would be worth, given the whole spirit of this discussion, separating out technical effectiveness from clinical effectiveness and to label this as a device that, with reasonable safety, has been shown to be technically effective

at retrieving particulate matter in the setting of cannulation of the aorta, but in a precaution sort of environment, or make a statement that while this has been shown to be technically effective at removing particular matter, it has not been shown to be clinically beneficial, and therefore, caution in the use of this device would be warranted.

DR. TRACY: I think it is difficult to go in that direction since we don't even know that it has been shown to be effective at removing particulate material. We don't know what percentage it is removing. I think that to introduce that into the labeling would be confusing, at the very least.

DR. KRUCOFF: I was actually just wondering from a precedent, because I can think back as far as a day where an indication for reducing ischemia during angioplasty was sort of a technical achievement that, actually, devices and biologics were both ultimately approved for, even though the full clinical ramifications of reducing ischemia as a technical feat were never implied or demonstrated. And I just wondered whether there was a precedent that we could get clearer language for docs who are considering using this in their

patients to make it very clear why this is on the market, but also the limitations of what we can understand about its clinical utility.

DR. TRACY: The study results are pretty clear as they are stated here. I think it doesn't have to be expanded beyond the study results. I think it is explained in here what the study results are, and I think it is fair to leave that open to interpretation for the operator whether that study results supports the use for them in their individual patients.

DR. AZIZ: If I could just make one point about the porcelain aorta, I think that shouldn't be put as a contraindication. I think I would just use it as a precaution, because you could probably see a case where you do a beating heart on-pump case where you won't cross-clamp the aorta, so you could still put the mesh inside.

So I would say that that should be a precaution but shouldn't be a contraindication.

DR. LASKEY: How about if you're just not willing to cross-clamp the aorta if it's a contraindication?

DR. FERGUSON: And I'll get back to the point again about the ECO--nobody wants to talk

about it--many times, you can't tell if you've got a porcelain aorta or not until you actually do the TEE. You don't want to do this, you don't want to do that, because that's going to be bad.

DR. TRACY: Shall we flip the page?

DR. MARLER: So, at least at a minimum, I hear that as a precaution, we could specifically notify the clinician that certain patients were excluded from the study, and there is no evidence of the safety in patients that--and then list the clinical exclusions.

DR. TRACY: I think it's very clear that more detailed description of clinical exclusion needs to be included in the labeling.

DR. MARLER: Rather than just referring to the protocol.

DR. TRACY: Right.

The next bullet, then, is: "Should the labeling include specific study information such as no reduction of clinical events were noted in a 1,289-patient clinical study; and the EMBOL-X device appears to increase the rate of endothelial injury?"

The study results on page 4 of 10 do indicate that none of the surgical procedure

differences between the randomized group achieved statistical significance. So that is there, I believe. And yes, I think it is important that those pieces of information be conveyed very clearly and in a fashion that can be readily picked up in the labeling.

And then, to grapple a little more with "What should the labeling include regarding the use of ultrasound both before--for assessment of the aorta--and after--monitoring of injury--the use of the device?" there are data provided on the use of TEE or epiaortic imaging, and that is presented on page 5. Is there something peculiar about this device that would make it necessary to mandate the use of TEE?

DR. FERGUSON: My suggestion would be something in the instructions for use of how helpful TEE can be in assessing the aorta both at the time the cannula is put in and also assessing the aorta before and after, but not to make it a mandatory part of the situation.

DR. TRACY: I think that's reasonable. It is stated here, but perhaps that could be clarified a little bit as to exactly what was seen with the two modalities of assessment, and then, certainly

in the instructions for use, that should be emphasized.

DR. LASKEY: What is the standard of care? Are all patients generally getting TEEs now?

DR. EDMUNDS: No. Could we go back to a previous slide? Number 2 of the first paragraph, you kind of went over, but I take objection to that statement, because "endothelial injury" is not defined. If you are going to use the term, I think you have to define it. We have discussed this, and we have been unable to demonstrate that this is a harmful finding, and we have shown, or the study showed, that 78 percent of OR personnel were unable to detect it at all.

So I think we have got to back off a little bit about that unless you start to raise a whole bunch of thorns that really don't need to be raised.

DR. TRACY: The thorns are there, though, unfortunately, and that was found, and it is defined on page 5 of 10, the presence of ecocardiographically-evident endothelial disruption is noted" and the statement is made "did not put the patient at a statistically greater risk for composite endpoint event." I think that's fairly

stated. It was there. There was no evidence that it increased the composite risk.

So it has to be there, and perhaps something that needs to be observed over time, because we certainly have very limited information about what the prognostic significance of this is, and in particular as more diseased aortas are approached with this device, I wouldn't be surprised if there were a greater risk of disruption in those patients. So we need to be tracking something like this.

Are there any other comments on this?

[No response.]

DR. TRACY: I think we are on to Number 5.

"Please provide any other recommendations or comments regarding the labeling of this device."

I think we touched on--Dr. Pina?

DR. PINA: I just want to go back and ask a question of the sponsor. Somewhere along the way, you stated that the endothelial injury was almost center-specific and operator-specific, or you saw it several times in the same operator, so that perhaps experience may have a lot to do with lack thereof.

Am I correct? Did I hear that right?

DR. TRACY: I don't think that was my impression.

DR. ALLEN: Actually, a good recollection. The two that were repaired were from the same center very early on in the experience, and then, after an historical basis for what we were seeing, and realizing they weren't causing clinical events, the additional 10 that were actually observed by surgeons weren't intervened on.

DR. PINA: Again, I don't know if it would pay to say something in there that, first of all, they are not that common. We don't know how many times this happens, as Dr. Edmunds said, and we don't even know about them. So something to take a little bit away from the fear, even though I know it is there, but not to cause undo alarm may have something to do with the experience of the surgeon or the surgeon's ability to see this, just to kind of temper a little bit the fear of the endothelial injury.

DR. TRACY: Wasn't it the repairs were done early on because people didn't understand the lack of clinical importance. It is not that the number of disruptions decreased over time.

DR. MARLER: Wait a minute, now.

Intuition is ruling today; right?
DR. TRACY: I'm sorry?
DR. MARLER: Emboli are bad. Endothelial injury is likewise bad. I don't see why there is any discussion of this.
DR. KRUCOFF: I think there is a reason, because I think you have to be fundamentally consistent about our assessment of the safety of the safety of this thing. To me, that's actually the much more rigorous part of this than the efficacy issue. And if we have all reached the consensus that this is safe, part of that is clearly based on our assessment that for the data presented, the significantly increased incidence of this finding in fact doesn't translate into significant clinical sequelae once, at least, you get enough competence in the surgical group to stop putting stitches into the darn things.
DR. TRACY: But I certainly wouldn't advocate removing page 5 of 10.
DR. PINA: No, no, I'm not advocating that, either.
DR. KRUCOFF: No, no. I think this is just consistent with what was brought up before about the statement if we are going to say

"endothelial injury," that implies something that is unsafe or bad. I think if we say this is a finding that has not appeared to translate into a clinically significant finding, that to me is consistent with our saying this is safe. And I think that's one where we can and need to be rigorous, particularly if we are unanimous.

DR. EDMUNDS: If you use the term "endothelial injury," detectable only on post-repair epiaortic ecocardiography one-quarter of the time that it is there by the OR personnel. In other words, I think this is totally impractical.

DR. TRACY: But it is there, and it is part of the description of the patient study. The phrase, I believe, is fair the way it is described, and I believe it should be left in the labeling. Okay.

Question 5. "Please provide any other recommendations or comments regarding the labeling of this device."

I think we along the course made other comments. Unless anybody else has additional comments to make regarding the labeling, I think we have covered this one.

Okay. And Question 6: "If the data provided are not adequate to support safety and/or effectiveness, what additional data analysis or study would you require?"

I think we are going to get back into the same discussion about what we need by safety and effectiveness. I think everybody would be happy if there were some other cognitive endpoint that could be analyzed at some point, obviously not in this dataset since it was not collected, but I think that would be something that we would be looking for in future studies, other measures that might be more appropriate than the composite endpoint that a priori is going to miss the thing that you are looking for, or you are hoping to reduce.

DR. ZUCKERMAN: Dr. Marler, can you be more specific regarding what measurements of neurocognitive dysfunction you would be looking for in future studies?

DR. MARLER: Given a menu, can I pick my favorite neuropsychological tests? Yes, I can. I like several tests because they are easy to administer, take little time, and cause minimal irritation to the patient and presumably the surgeon.

But I think that we have found it possible in the research that I have sponsored in this from Wake Forest and now Johns Hopkins that if you put them in a room and don't let them out, it gives them specified limits that a neuropsychologist can reach some agreement on how to do neuropsychological evaluation in an efficient and cost-effective way.

It is not answering your question, but to say Trailmaking B or Trailmaking A or this or that test I don't think is helpful in this situation. I think there is a way to come up with cognitive evaluation, and I think it has been done before, and I think it would move the field forward.

You read different things in the newspaper from year to year. Sometimes it has cognitive effects, and I think most recently in the newspaper, it doesn't, at least, long-term effects.

Sorry to be so unhelpful. I think it is a question that can be answered; I'm not going to answer it now.

DR. TRACY: The other piece of effectiveness is what percentage of material is the device capturing. And it seems like there might be some other bench test that could be better designed

other than non-sticky things being passed through the system. There must be some other biologic way of testing to get a better idea of what percentage of material is being missed or picked up by the device.

I would suggest that being part of the mechanical effectiveness assessment that should be done. And I am still a little troubled by your original question about is there some design problem here with the device that is resulting in whatever these disruptions are. We need to somewhere along the line satisfy the FDA on that with this device and certainly with any future device.

Dr. Krucoff?

DR. KRUCOFF: I would also suggest at least for future work, because I think one of the things that Chris mentioned that we have seen in other filters, since these are circular devices, and whether they are aligned, whether they are rotationally aligned and actually transverse across the aorta or whether they are cockeyed, that at that level, if there were a way--imaging or otherwise--to get a sense of how frequently these things simply are or are not aligned the way you

would ideally envision them, to me, that would be useful information somewhere along the line in the evolution of these things.

DR. MARLER: I wanted to add to my comment that my intuition--since intuition is important today--is that the way to find effects on the brain is not to look at low-risk patients but to include patients who have had prior stroke, have atrial fibrillation, have high risk of stroke, and they are usually the ones who show the effects of interventions. It is easier to see an effect.

I would say that what you have is the baseline stroke rate that goes with the whole procedure here, and there was no increase or decrease, but in particularly risky patients, you might be more likely to see the cognitive effects and the stroke effects. That is based on a number of trials that I am saying that.

DR. AZIZ: I think the problem with that would be to read lighting up of the stroke in those patients may be unrelated to emboli. It may be hypertensive episodes. So the protective effects--

DR. MARLER: We are having increasing evidence--well, okay--stroke is a systemic problem, and what triggers it varies from individual and

from time to time, and what we are seeing here is these emboli may be more of a trigger of a whole cascade of events rather than the entire event itself.

DR. EDMUNDS: I think this will come out if this is approved and used over time, but we don't have the data to say anything about it now, and that's why I think we have to wait. But I'm sure that clinicians will want to use it in the high-risk patients; it's just horse sense.

DR. MARLER: I'm just trying to provide advice where I would go if I had to find clinical benefit. I am saying that the higher-risk patients, certainly with cognitive measures, but go where the things are happening.

DR. TRACY: Are there any other comments on this question?

DR. FERGUSON: I have one question. With the PMAs, we talk a lot about post-market approval studies. That is not an issue with the 510(k) as I understand; right?

DR. ZUCKERMAN: That's correct.

DR. FERGUSON: Thank you very much.

DR. TRACY: Are there additional questions or comments that the FDA would like to make?

DR. ZUCKERMAN: No.
DR. TRACY: Does the sponsor have any additional comments or questions at this time?
MS. CHANG: No, thank you.
DR. TRACY: Mr. Dacey, any comments or questions?
MR. DACEY: After over 4 years, this is my first 510(k) experience, and I certainly can't bring any clinical experience or intuition to this process, but speaking for the consumer, I am awfully glad that this process is taking place.
That's all that I have to say.
DR. TRACY: Thank you.
I guess Mr. Morton, by the fact that he is not here, apparently has no additional comments.
So at this point, we will have another open public hearing.
Is there anyone in the audience who wishes to address the panel on today's topic?
[No response.]
DR. TRACY: If not, we'll close the open public hearing.
Are there any final recommendations from the panel?
[No response.]

DR. TRACY: Dr. Zuckerman?
DR. ZUCKERMAN: Geretta, do you have something to read about finding out about each panel participant's view on this topic?
MS. WOOD: No.
DR. ZUCKERMAN: I stand corrected. Thank you.
DR. TRACY: I think you heard them.
The meeting is adjourned.
Thank you all very much.
[Whereupon, at 3:42 p.m., the proceedings were concluded.]

- - -